Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2002; 5 (2), 171-177

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

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Pharmacologic Bridging With Prostaglandin E1 Before Heart Transplantation – A New Chance for an Old Drug

Brigitte Stanek

In everyday practice, physicians consider heart failure refractory when intractable signs and symptoms (oedema, pulmonary congestion, dyspnoea, fatigue) occur although vigorous attempts have been made to adjust oral heart failure therapy. This condition is present in about 15 to 20 % of heart failure patients and is associated with high mortality unless heart transplantation (HTx) is performed. However, during the waiting period, decompensation is frequent and need of hospitalisation increases steeply. In this population, intravenous infusions with inotropes or vasodilators, such as prostaglandin E1 (PGE1), elicit similar dramatic effects when given acutely. Patients who face a longer wait on the HTx list, may be considered for long-term intravenous PGE1 therapy in an attempt to facilitate hospital discharge. As a rule, to qualify for bridging with PGE1 patients must be receiving maximum tailored therapy with digoxin, diuretics, and ACE-inhibitors (or analogous drugs) while hospitalised. Further, a positive haemodynamic response to PGE1 during right heart catheterization is required. PGE1 ambulatory infusions are easily administered with a pump through central venous tunnelled access lines and can be given after a brief period of instruction with few readmissions or significant complications. A prospective randomized trial suggested increased freedom from worsening heart failure in patients bridged with PGE1 as opposed to prostacyclin or dobutamine. Finally, patients bridged with PGE1 appear to have similar 1-year-survival rates after HTx as patients receiving oral heart failure medications only. *J Clin Basic Cardiol 2002; 5: 171–7.*

Key words: prostaglandin E1, refractory heart failure, heart transplantation, bridging therapy, outcome

Prostaglandin E1 (PGE1) or alprostadil is a naturally occurring prostaglandin vasodilator of the E-series isolated in 1962 [1–3]. Based on its potent pharmacological effects in the pulmonary circulation, a variety of applications in intensive care medicine was soon thereafter evolved, including primary pulmonary hypertension, chronic obstructive pulmonary disease, cardiogenic pulmonary hypertension and acute right heart failure [4–9]. However, PGE1 was also used in intensive care medicine as a peripheral vasodilator in left ventricular failure, in particular in patients with ischaemic heart disease or following myocardial infarction [10–12]. In addition, peripheral occlusive disease emerged early as a promising new field [13, 14].

Traditional Role of PGE1 in Transplant Medicine

Since heart transplantation (HTx) became an option for patients with endstage heart failure in our center 15 years ago, a new chance for PGE1 emerged. Clearly, cardiac decompensation in patients with endstage heart failure is a phenomenon of diverse causes. As increase in pulmonary resistance is a normal response to left ventricular dysfunction, the clinical picture usually includes failure of both the left and the right ventricle. The severity of pulmonary resistance may have major implications regarding the patient's response to various modes of therapy. While passive elevations in pulmonary artery pressure due to "backward" transmission of increased left ventricular filling pressure may be controlled with dobutamine in some patients, in others pulmonary hypertension persists. This is particularly intriguing in the context of HTx because of the vulnerability of the right ventricle of the donor heart. If high pulmonary resistance was a consequence of abnormally increased pulmonary vascular reactivity, it could be reversed by PGE1 within hours to days [15–19]. Thus, it was recognized that the impact of PGE1 on the pulmonary circulation of HTx candidates and recipients is of major importance. However, other patients who decompensated on the waiting list were also potential candidates for PGE1 [20].

Haemodynamic Pilot Studies

To create a scientific basis for the use of PGE1 in such patients, a series of pilot studies was performed [21]. In catecholamine-dependent patients who were refractory to optimized oral therapy, coadministration of PGE1 to dobutamine and dopamine yielded an additional haemodynamic benefit with reduction of filling pressures and a further 20 % increase in stroke volume [22]. In a formal placebo-controlled double-blind study, the effects of PGE1 on pulmonary artery pressure, pulmonary vascular resistance, stroke volume and cardiac output were significantly different from placebo [23]. Furthermore, short-term effects of PGE1 or nitroglycerin infusions were compared in ambulatory patients with advanced heart failure. Both vasodilators resulted in a comparable reduction of filling pressures, but only PGE1 increased cardiac output. Moreover, by simultaneous magnetic resonance tomography, PGE was shown to reduce endsystolic and enddiastolic ventricular diameters [24, 25]. These results accorded with previously published data obtained with PGE1 in a combined haemodynamic Doppler evaluation [26]. Besides expected reductions in afterload of both ventricles (with a more pronounced effect on pulmonary compared to systemic vascular resistance), PGE1 reduced left ventricular enddiastolic pressure by 21 %.

Dose-Effect Relationships of PGE1

To evaluate the time sequence and magnitude of PGE1's haemodynamic effects, a dose finding study was performed [27]. The first significant change was a 20 % decrease in systemic vascular resistance index accompanied by a 18 % increase in cardiac output at an infusion rate of 2.5 ng/kg/min, which was sustained at 5 ng/kg/min PGE1 in all 24 patients. A dose response-curve with cumulative doses up to 25 ng/kg/min PGE, could be set up in a subset of 14 patients who tolerated up-titration without side effects. The beneficial changes observed with low dosages of PGE1 were sustained up to the maximal dose. Importantly, with 15 and 20 ng/kg/min PGE1

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blood pressure decreased, but only by 4 mmHg. Then the effects of maximal tolerated dosages of PGE1 were evaluated in two subsets using a dose of 20 ng/kg/min as a cut-point (14 patients tolerated 34 ± 2 ng/kg/min PGE1, 10 patients tolerated 15 ± 2 ng/kg/min). No significant difference in the haemodynamic response to PGE1 was detected. Subsequently, these individually found dosages were halved for continuous infusion over 12 hours. The results demonstrated potent haemodynamic effects in the low-dose subset as well. While systemic effects appeared rapidly, a slower onset of the pulmonary effects with a significant reduction in pulmonary vascular resistance by an average of 28 % was observed.

Observational Experience with Chronic PGE1

Observation provided the basis for bridging patients to HTx with chronic PGE1 infusions [28]. Continuous infusions of 5 mcg/kg/min dobutamine and 3 mcg/kg/min dopamine were then considered as traditional standard in our institution. A first series of 65 patients, including 15 patients listed at the urgent request mode received only catecholamines (11 patients) or PGE1 on top of both catecholamines or combined with dopamine only (54 patients). PGE1 infusion rate was individually adjusted according to a protocol assessing haemodynamic effects at maximum tolerated dose (average 29 ng/kg/min). This dose was subsequently halved for continuous infusion through in-dwelling central venous lines connected to automatic pumps. 54 % of patients bridged with PGE1 were dismissed for home infusions. After 1 month the acute increase in cardiac output was sustained although the dose was further reduced to average 8 ng/kg/min. Worsening heart failure was observed in 5 patients receiving catecholamines without PGE1. In patients receiving PGE1, serum creatinine increased in 3, rather reflecting severity of heart failure than a PGE1-associated side effect. Forty-two patients underwent HTx, and 17 patients died. The remaining 6 patients recovered and were weaned from bridging therapy [29]. In another combined neurohumoral haemodynamic pilot study, 13 patients received "single" PGE1 infusions [30]. In the acute PGE1 challenge test (average dose 26 ng/kg/min) the typical reaction pattern of a balanced vasodilator was observed with a drop in blood pressure, right atrial pressure, pulmonary artery pressure and pulmonary wedge pressure and a rise in stroke volume and cardiac output. Heart rate remained constant. Plasma levels of atrial natriuretic peptide decreased, while plasma norepinephrine and big endothelin were unchanged. After 4 weeks (average dose 8 ng/kg/min), the beneficial effect on cardiac output and pulmonary resistance was sustained and relief of symptoms was recorded in all but one patients.

Table 1. Clinical characteristics, preoperative risk factors, complications and 1-year survival after heart transplantation for the three study groups

Variable	Group 1 (n = 438)	Group 2 (n = 50)	Group 3 (n = 108)
Recipient age (y)	50 ± 12	50 ± 12	47 ± 13
Recipient sex (m/f)	362/76	46/4	94/14
Diagnosis (IHD/DCM)	143/295	14/36	33/75
Pretransplant intensive care unit (n)*	2 (0.5 %)	17 (34 %)	79 (73 %)
LVEF (%)*	17 ± 8	14 ± 6	16 ± 8
Cardiac index (L/min/m^2)	2.5 ± 6	1.8 ± 0.4	2.3 ± 0.8
PAOP (mmHg)	25 ± 9	28 ± 7	26 ± 9
PAMP (mmHg)*	34 ± 11	39 ± 8	36 ± 10
Wood (mmHg/L/min)*	2.6 ± 1.4	3.6 ± 2	2.9 ± 1.7
Waiting time (d)*	124 ± 123	85 ± 80	44 ± 64
Donor age (y)*	31 ± 12	35 ± 11	31 ± 11
Sex mismatch (n)	127 (29 %)	10 (20 %)	33 (31 %)
Ischaemic time (min)*	155 ± 54	192 ± 46	149 ± 58
Perioperative blood units*	3.5 ± 6.3	3.3 ± 4.0	5.5 ± 8.0
ECC time (min)*	146 ± 64	178 ± 43	136 ± 57
Acute renal failure (n)*	17 (4 %)	1 (2 %)	15 (14 %)
Intubation time (d)	1.9 ± 2.7	2.1 ± 1.7	2.6 ± 5.4
Stay in intensive care unit (d)*	5.2 ± 5.3	4.3 ± 2.3	9.1 ± 9.5
Perioperative mortality (n)	45 (10 %)	6 (12 %)	17 (16 %)
1-year mortality (n)*	76 (17 %)	9 (18 %)	39 (36 %)
1-year infection rate (n)*	110 (24 %)	17 (34 %)	41 (37 %)
1-year rejection rate (n)*	72 (16 %)	7 (14 %)	12 (11 %)

Group 1 received oral medications only, group 2 received additional PGE1, group 3 received inotropic support without PGE1. DCM = dilated cardiomyopathy, ECC = extracorporeal circulation, IHD = ischaemic heart disease, LVEF = left ventricular ejection fraction, PAOP = pulmonary arterial occlusion pressure, PAMP = pulmonary arterial mean pressure; *$P < 0.05$. Reprinted from Transplantation Proceedings, 31, B. Frey et al., Effects of continuous, long-term therapy with prostaglandin E1 preoperatively on outcome after heart transplantation, 80–81, © 1999, with permission from Elsevier Science [31].

Outcome

In a large data base study of 596 patients who were transplanted between 1984 and 1996 in our center, the overall outcome was evaluated [31]. Patients were stratified according to their severity of heart failure when evaluated for HTx listing. 438 patients were stable and maintained on oral medications, 50 patients had refractory heart failure and received PGE1 for bridging, and 108 patients were treated with i.v. dobutamine without PGE1. Main endpoints of the study were perioperative morbidity and mortality and one-year posttransplant survival (Tab. 1).

In the PGE1 group mean pulmonary pressure was higher compared with the dobutamine group. The waiting time on the list, however, was longer. Despite this, only 34 % awaited HTx as inpatients in an ICU compared with 73 % on dobutamine. Dobutamine patients also had the highest

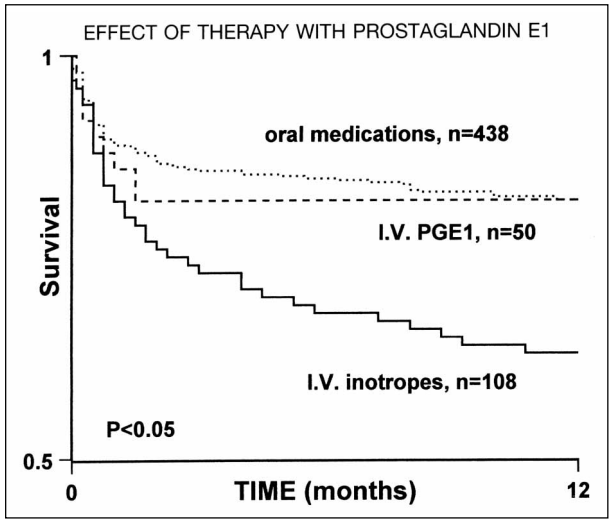

Figure 1. Kaplan-Meier lifetime analysis of survival in 596 patients who underwent their first heart transplantation, stratified according to their preoperative heart failure therapy. Reprinted from Transplantation Proceedings, 31, B. Frey et al., Effects of continuous, long-term therapy with prostaglandin E1 preoperatively on outcome after heart transplantation, 80–81, © 1999, with permission from Elsevier Science [31].

perioperative complication rate. They required more intraoperative blood units, had a higher incidence of postoperative acute renal failure, and stayed longer at the ICU. Perioperative mortality did not differ significantly, however. One year mortality rates were 17 % in non-bridged patients, 18 % for PGE1 bridged patients and 36 % for dobutamine bridged patients. The findings suggested that bridging refractory patients with PGE1 enables successful HTx (Fig. 1).

In another prognostic substudy the acute haemodynamic benefits of PGE1 on right ventricular performance were investigated [32]. It was hypothesized that the degree of impaired loading of the right heart might be related to outcome. Sixty-eight patients with refractory heart failure in low cardiac output of average 1.7 L/min/m^2 with high average pulmonary wedge pressure of average 25 mmHg receiving PGE1 either alone or combined with 5 mcg/kg/min dobutamine and in need of urgent HTx at referral were included. Patients were followed for one year. At the end of the observation period 31 patients were stable on the list over average 219 days while receiving PGE1 or after weaning or had been electively transplanted after down-ranking to non-urgent status after at least 90 days. 37 patients who died or experienced recurrent decompensation and were urgently transplanted after average 50 days. Right ventricular parameters included ejection fraction as well as end-diastolic and end-systolic volumes. Two hours after oral medications PGE1 infusion was up-titrated to 23 ng/kg/min and 27 ng/kg/min respectively according to side effect limit and then reduced to 50 % for continuous infusion. 75 % of the patients could be discharged for home therapy. Haemodynamic parameters at entry were similar in both outcome groups. Under maximal vasodilatation with PGE, however, systemic vascular resistance and enddiastolic volume index were different. In addition, atrial natriuretic peptide levels were positively correlated to right ventricular volumes and changes in the latter were followed by rapid alterations in these cardiac hormones [25]. This phenomenon was registered in patients with a positive outcome but not in patients who died or deteriorated clinically (Tab. 2).

Table 2. Haemodynamic variables

	Group A		Group B	
	Baseline	MTD	Baseline	MTD
MTD of PGE1 (ng/kg/min)	–	23 ± 10	–	27 ± 10
HR (beats/min)	84 ± 16	95 ± 35*	86 ± 21	90 ± 20
RR mean (mmHg)	78 ± 10	70 ± 17*	73 ± 10	64 ± 8****
RAP (mmHg)	10 ± 5	9 ± 4**	10 ± 5	9 ± 6
PAPm (mmHg)	39 ± 9	36 ± 6	38 ± 6	36 ± 7*
PCwP (mmHg)	25 ± 5	21 ± 6***	25 ± 6	22 ± 7*
CI (liter/min/m^2)	1.7 ± 0.4	2.3 ± 0.7***	1.8 ± 0.4	2.5 ± 0.7****
SVI (ml/m^2)	22 ± 9	27 ± 11**	23 ± 8	30 ± 11****
SVRI (dyn×sec/cm^5×m^2)	3272 ± 1055	2331 ± 950****	2872 ± 803	1877 ± 640****
PVRI (dyn×sec/cm^5×m^2)	637 ± 261	544 ± 223**	595 ± 200	485 ± 220***
REF (%)	12 ± 4	16 ± 6****	13 ± 6	16 ± 6**
EDVI (ml/m^2)	196 ± 68	173 ± 51**	188 ± 52	197 ± 42
ESVI (ml/m^2)	175 ± 67	147 ± 48**	165 ± 53	167 ± 42

CI = cardiac index, HR = heart rate, MTD = maximum tolerated dose of prostaglandin E1 (PGE1), PAP = pulmonary arterial pressure, PCwP = pulmonary capillary wedge pressure, PVRI = pulmonary vascular resistance index, RAP = right arterial pressure, RR = arterial blood pressure, SVI = stroke volume index, SVRI = systemic vascular resistance index, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ within a group. Reprinted from J Heart Lung Transplant, 19, M. Hülsmann et al., Response of right ventricular function to prostaglandin E1 infusion predicts outcome for severe chronic heart failure patients awaiting urgent transplantation, 939–945, © 2000, with permission from Elsevier Science [32].

Responder and nonresponder were defined as a decrease in enddiastolic volume index of more or less than 10 % at peak PGE dose. Seventeen of 21 patients who had decreases of more than 10 % improved and 33 of 47 patients who had decreases of less than 10 % could not be stabilized. The sensitivity and specificity of prediction was 89 % and 70 % respectively. Estimates of combined death or worsening heart failure were significantly different between responders and nonresponders (Fig. 2).

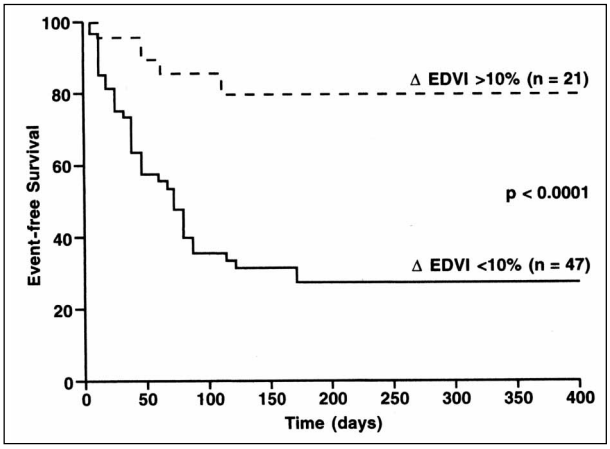

Figure 2. Kaplan-Meier analysis showing cumulative rates of event-free survival in 68 patients with congestive heart failure stratified in 2 groups based on EDVI decrease under PGE1-infusion. Patients with a decrease EDVI by > 10 % differed significantly from patients with a lesser decrease. EDVI = end-diastolic ventricular index, PGE1 = prostaglandin E1. Reprinted from J Heart Lung Transplant, 19, M. Hülsmann et al., Response of right ventricular function to prostaglandin E1 infusion predicts outcome for severe chronic heart failure patients awaiting urgent transplantation, 939–945, © 2000, with permission from Elsevier Science [32].

Prospective Comparative Trials of PGE

Placebo-controlled trial

The basis of evidence supporting the use of PGE1 as a bridging drug is difficult to obtain. The problem is that the use of other bridging agents is also based on experience rather than evidence. [33]. Both dobutamine and prostacyclin, despite some theoretical rationale, have been shown in placebo-controlled trials to increase mortality in patients lacking the current option of HTx or in nontransplantable patients. To apply the gold standard of placebo for evaluating pharmacologic agents to urgent indications is questionable. Accordingly, we have limited our placebo controlled comparison of PGE1 (average 16 ng/kg/min) and dobutamine (average 4.5 mcg/kg/min) and placebo to 7 days, and included only patients in whom this procedure seemed acceptable [34]. With both drugs blood pressure was sustained while significant drops of filling pressures and systemic vascular resistance accompanied by a rise in flow were recorded acutely, at 12 hours and after 7 days when also pulmonary vascular resistance was reduced. Placebo decreased right atrial pressure slightly. PGE1 and

dobutamine similarly enhanced renal plasma flow after 7 days, without affecting glomerular filtration rate. However, only PGE1 decreased filtration fraction. Placebo had no effect. The trial suggested that in advanced heart failure PGE1 and low-dose dobutamine are similarly effective in improving haemodynamics and renal perfusion. PGE1 may have the favourable potential to maintain filtration at lower intraglomerular pressure (Fig. 3).

Longitudinal Bridging Trial

Original study

To gain information concerning the use of PGE1 as a single bridge-to-HTx a head to head comparison was performed with low-dose dobutamine and prostacyclin (flolan) to evaluate the respective clinical outcomes [33]. The PGE1 arm and the dobutamine arm enrolled 30 patients each, while the prostacyclin arm was truncated after 8 patients. The inclusion of prostacyclin was based on the premise that both PGE1 and prostacyclin (flolan) were previously used in heart failure patients based on their potent haemodynamic effects. Unfortunately, flolan increased mortality in the FIRST study, predominantly from worsening heart failure. A rigorously selected cohort of 68 ambulatory elective HTx candidates (8 women) was included, all in refractory chronic heart failure despite efforts to optimize oral medications for at least one month, with average left ventricular ejection fraction of 14 %. None had required intravenous inotropes/vasodilators previously, or had unstable angina, aortic stenosis, or progressive renal disease. Unless implanted with a cardioverter defibrillator, patients with a history of ventricular tachycardia, fibrillation, or aborted sudden death were unacceptable.

Design

A combined endpoint consisting of 3 parts was defined for the effect of bridging, all cause mortality, failure to prevent heart failure from worsening, and serious adverse events such as malignant ventricular or sustained atrial tachycardias. Predictable prostaglandin-related side effects such as myalgia, athralgia, headache, or nausea were controlled by dose reduction. For patients with non-fatal events admittance to the intensive care unit and uplisting with higher priority status was provided. The bridging study was preceded by a dose finding phase for which haemodynamic stabilization was chosen as endpoint. Each intravenous regimen was required to increase cardiac output by 20 % or more and to reduce pulmonary vascular resistance below 550 dyn × s/cm^{-5} × m^{-2}.

Outcome

Since this predefined haemodynamic goal was failed by 21 patients, only 47 patients were available for the longitudinal trial. Of these, 26 patients were bridged with PGE1 for average 88 days, with 7 patients (27 %) reaching an endpoint. Seventeen patients received dobutamine for average 30 days with 12 patients (72 %) reaching an endpoint. Prostacyclin was used in only 4 patients, all reaching an endpoint. The most interesting endpoints in regard to the management of patients on the waiting list, haemodynamic stabilization and worsening heart failure during long-term therapy were summarized by treatment group and compared in a Kaplan Meier analysis. The findings from this prospective open pilot trial suggest that continuous PGE1-infusions at individualized dosages can be useful in certain patients as a pharmacologic bridging procedure with reduced risk to develop worsening

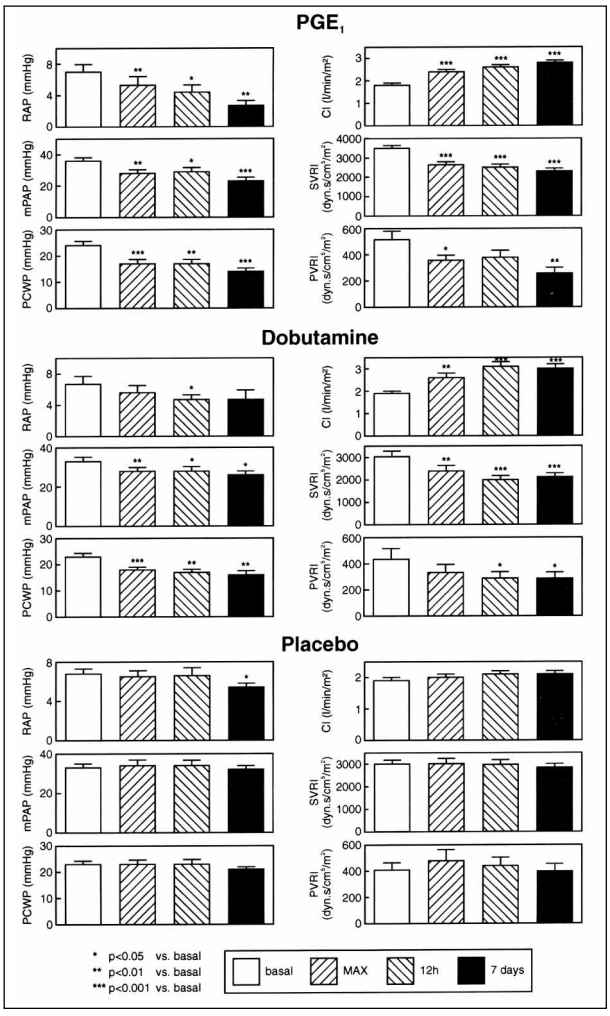

Figure 3. Mean values ± SEM of right arterial pressure (RAP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) before (baseline) at maximal dose (max) after 12 hours (12 h) and 7 days after continuous infusion of prostaglandin E1 (PGE1, n = 10), dobutamine (n = 10) or placebo. Reprinted from [34] with permission from Japanese Heart Journal Association, © 1999.

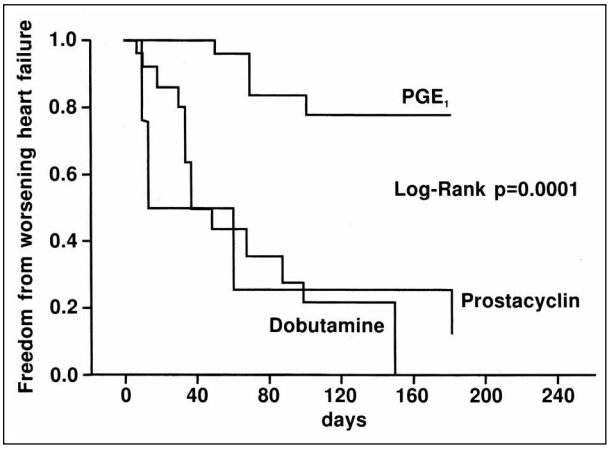

Figure 4. Kaplan-Meier analysis showing cumulative rates of event-free survival (freedom from worsening heart failure in 3 study groups). Reprinted from J Heart Lung Transplant, 18, B. Stanek et al., Bridging to heart transplantation: prostaglandin E1 versus prostacyclin versus dobutamine, 358–366, © 1999, with permission from Elsevier Science [33].

Table 3. Effects of continuous, long-term treatment with PGE1 on haemodynamic variables*

	PGE1			Dobutamine		
Variables	Baseline (n = 21)	12 h (n = 21)	4 wk (n = 21)	Baseline (n = 11)	12 h (n = 11)	4 wk (n = 11)
HR (beats/min)	84.0 ± 18.2	86.0 ± 20.6	81.0 ± 13.8	83.8 ± 18.2	89.0 ± 14.3	78.0 ± 15.6
RR mean (mmHg)	79.3 ± 12.8	67.9 ± 9.0#	75.7 ± 9.4	77.0 ± 9.4	68.5 ± 5.0#	79.6 ± 11.6
RAP mean (mmHg)	9.7 ± 4.6	6.5 ± 4.0#	9.7 ± 4.0	9.0 ± 5.4	5.3 ± 4.2#	9.6 ± 4.4
PAP meam (mmHg)	37.6 ± 5.8	30.4 ± 6.3#	35.3 ± 9.5	39.4 ± 6.5	31.8 ± 7.0#	37.4 ± 7.1
PCwP (mmHg)	25.3 ± 3.4	16.5 ± 4.7#	23.8 ± 6.8	24.2 ± 3.8	18.2 ± 5.3#	25.8 ± 6.8
CI (litre/min/m^2)	1.7 ± 0.4	2.6 ± 0.6#	2.5 ± 0.6#	1.8 ± 0.3	2.8 ± 0.4#	2.3 ± 0.6#
SVRI (dyn×sec/cm^5×m^2)	3352 ± 954	1957 ± 582#	2178 ± 519#	3049 ± 814	1858 ± 344#	2565 ± 809
PVRI (dyn×sec/cm^5×m^2)	593 ± 300	436 ± 145#	390 ± 253#	680 ± 392	392 ± 160#	431 ± 184

CI = cardiac index, HR = heart rate, PAP = pulmonary arterial pressure, PCwP = pulmonary capillary wedge pressure, PVRI = pulmonary vascular resistance index, RAP = right arterial pressure, RR = arterial blood pressure, SVRI = systemic vascular resistance index
*Values given as mean ± SD, #$P < 0.05$ compared to baseline. Reprinted from [37], with permission from CHEST, © 2000.

heart failure before HTx. Bridging therapy, confined to patients with heart failure that is refractory to aggressive oral treatment, is hence targeted to obtain symptom relief during the waiting period for HTx spent at home rather than in hospitals. Despite valuable haemodynamic effects of dobutamine, lasting clinical benefit without unacceptable side effects was rather achieved with continuous infusions of PGE1 in this specific cohort (Fig. 4).

Three separate substudies evaluated haemodynamic effects of patients receiving PGE1 compared with prostacyclin [35] or with dobutamine [36, 37] In two of them neurohumoral effects were also evaluated.

Substudy 1
In the comparison with prostacyclin, average peak dose was 21 ng/kg/min for PGE1 in 10 patients and 7 ng/kg/min for prostacyclin in 8 patients. The doses were halved for continuous infusion. In the acute study, both agents increased cardiac output with constant heart rate, but only prostacyclin induced hypotension and increased plasma norepinephrine. After 12 hours filling pressures decreased further in parallel with plasma atrial natriuretic peptide levels and the rise in cardiac index remained. In contrast, with prostacyclin right atrial pressure increased and cardiac output fell. Thus, only the acute central haemodynamic effects of the two vasodilators were comparable in magnitude and direction, with stronger peripheral actions of prostacyclin which triggered unfavourable adrenergic counterregulation. With prolonged administration of these drugs at reduced dosages, however, desired haemodynamic changes appear to be sustained with PGE1 only.

Table 4. Changes in plasma big endothelin in patients with event-free survival compared with patients who had poor outcomes*

	Plasma big endothelin, fmol/mL	
Time	Event-free survival (n = 19)	Poor outcome (n = 13)
Baseline	6.6 ± 2.9	8.1 ± 3.8
1 wk	4.5 ± 1.9	5.1 ± 1.9
2 wk	4.5 ± 2.9	6.2 ± 2.0
3 wk	4.9 ± 2.8	6.5 ± 2.0
4 wk	3.7 ± 1.5	6.3 ± 3.0

*Values given as mean ± SD. Baseline values did not differ between the two groups. On repeated-measures ANOVA, the treatment effect between groups is statistically significant ($p < 0.05$). In addition, the treatment effect over time is statistically significant in both groups ($p < 0.001$). Reprinted from [37], with permission from CHEST, © 2000.

Substudy 2
In the second substudy data from 10 patients who were randomised to dobutamine were compared with data obtained with PGE1 throughout 12 hours [36]. Dobutamine was administered at a mean dose of 4.5 mcg/kg/min which was needed to achieve a 20 % increase in cardiac output and which was maintained throughout. After 12 hours PGE1 and dobutamine decreased pulmonary vascular resistance by average 26 % and by 29 %, and systemic vascular resistance by average 46 % and 25 %, respectively. Cardiac output was enhanced substantially, by average 68 % with PGE1 and by 47 % with dobutamine. In addition, PGE1 reduced pulmonary artery pressure by 20 % and systemic blood pressure by 15 %. Thus, in patients requiring intravenous support, PGE1 and dobutamine were similarly effective in stabilizing the haemodynamic condition within 12 hours.

Substudy 3
The third substudy of patients who participated in the PGE1 or dobutamine arm for a minimum of 4 weeks evaluated data obtained from repeat right-heart catheterization as well as from serial plasma big endothelin levels [37]. After 12 h of therapy, mean arterial blood pressure, right atrial mean pressure, pulmonary artery mean pressure, pulmonary wedge pressure, systemic vascular resistance index and pulmonary vascular resistance index all decreased in both treatment groups and cardiac index increased. After 4 weeks of therapy, the increase in cardiac index was sustained in both groups, whereas the decreases in the systemic and pulmonary vascular resistance indices were sustained in the PGE1 treatment group only. These changes reflected the typical potent systemic and pulmonary vasodilator effects of PGE (Tab. 3).

Prediction of Future Events

Changes in haemodynamic variables were also assessed and compared in 19 patients with future event free survival versus 13 patients who suffered a serious event after 4 weeks of treatment. At baseline, the outcome groups were comparable with respect to any haemodynamic variable. After 12 hours of continuous treatment, mean blood pressure, right atrial mean pressure, pulmonary artery mean pressure, pulmonary wedge pressure, systemic vascular resistance index and pulmonary vascular resistance index all decreased and cardiac index increased and after 4 weeks, a significant increase in cardiac index and decrease in systemic vascular resistance were sustained in both outcome groups. However, the changes in both cardiac index and systemic vascular resistance were significantly different. Furthermore, the decrease in pulmonary

artery pressure and in pulmonary vascular resistance was sustained only in patients who were event-free. These desirable effects were accompanied by a gradual drop in big endothelin plasma levels (Tab. 4).

In multivariate analysis, no baseline parameter was found to contribute to prognosis of these patients. In contrast, 2 parameters measured after 4 weeks of treatment for plasma big endothelin and systemic vascular resistance index, were associated with improved outcomes and provided independent prognostic information. Thereby plasma big endothelin with an arbitrary cut-off value of 4.3 fmol/ml accurately predicting future events in 72 % of the patients, was a stronger predictive marker than a reduction in peripheral vascular resistance index to < 2300 dyne s cm-5/m2. Conversely, persistently elevated plasma big endothelin levels within a period of 4 weeks and/or a persistently elevated peripheral vascular resistance strongly suggest a poor prognosis in the absence of symptoms that are suggestive of impending decompensation. Heart failure is a vasoconstrictive state due to a variety of factors such as the abnormal imbalance of endothelial dilator/constrictor forces, norepinephrine, angiotensin II, and vasopressin. Accordingly, peripheral resistance would not simply reflect a single vasoconstrictor system but has prognostic significance on its own. Improved left ventricular loading conditions and a better haemodynamic profile resulting from continuous treatment are probably the major mechanisms for lowering big endothelin plasma levels [38] (Fig. 5).

Rationale for the Long-term Use of PGE1 Prior to HTx

Based on the notion that symptoms in end-stage heart failure are not only determined by left ventricular dysfunction but also by right ventricular dysfunction, PGE1 infusions as bridging therapy appear particularly attractive. PGE1 provides an additional favourable haemodynamic effect when compared to nitrates in regard to cardiac output and to dobutamine in regard to pulmonary pressure. Data both in animals and in man suggest that PGE1 dilates nearly all peripheral arteries and increases the blood flow to the organs , although the intensity of the effect varies [39]. In physiologic terms this vasodilator effect enables a regulatory function which may serve to maintain blood flow to vital organs such as the kidney. Among a broad spectrum of other actions in the vessel wall, these compounds preserve endothelial integrity, capillary tone, and permeability [40, 41]. Moreover, PGE1 is also a neurohumoral antagonist based on its potential to blunt the activity of the sympathetic nervous system [42–44]. Downregulation of the production of toxic cytokines was also demonstrated which could be associated with the reduction of fibrosis thus adding a structural "biologic" component to its actions [45, 46]. Development of fibrosis via cytokines might be involved in the fixed component of pulmonary hypertension which cannot be expected to be relieved in the same manner as the reversible component after HTx [47]. However there is also a role for fibrosis in right ventricular dysfunction [48–50]. To elucidate the potential structural effects of PGE1 in heart failure appropriately designed studies have to be performed.

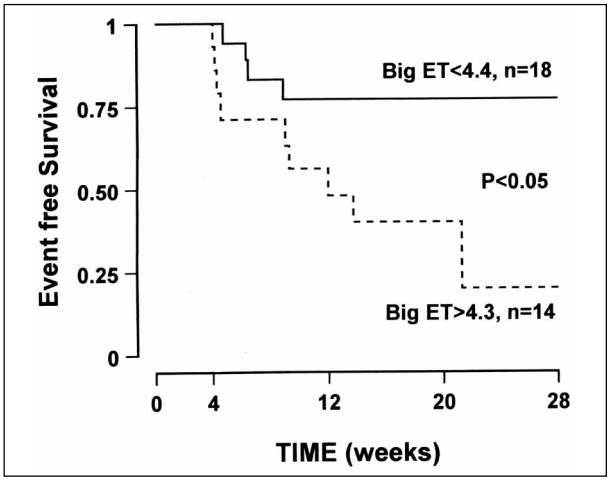

Figure 5. Kaplan-Meier analysis showing event-free survival in 32 listed candidates for heart transplantation after 4 weeks of ambulatory, continuous, long-term IV therapy. Patients were stratified into 2 groups according to plasma big endothelin levels after 4 weeks of uneventful therapy. Patients with lower plasma big endothelin levels had significantly better outcomes ($p < 0.05$). Reprinted from [37], with permission from CHEST, © 2000.

Patient Definition for PGE1 Bridging Therapy

In common sense, chronic heart failure patients are considered refractory if symptoms remain at rest and patients suffer from severe dyspnoea and fatigue. Immediate intravenous support in such patients appears mandatory for symptom relief. Refractory in whose hands, however? Have all available oral medications been administered as recommended [51–53]? Are formal haemodynamic measurements available to confirm this diagnosis? For the use of PGE1, patients should be carefully selected and the indication should be strictly defined. PGE1 infusions have to be introduced under invasive haemodynamic monitoring to document the suspected low cardiac output (threshold 2.5 L/min/m2) despite elevated left ventricular filling pressures (threshold 20 mmHg) before its use. The expertise and experience required for successful application restricts this therapy to specific centers because the use of PGE1 in HTx candidates warrants elaborate monitoring. A team of physicians from our unit instructed the patients and their relatives in central venous line care, handling of the infusion pump, and in sterile preparation of the drug solution. In case of problems, the patients could call their medical supervisor at any time. Patients were followed up every week in the outpatient unit where therapy was individually adjusted [54].

By definition the term "refractory heart failure" has to be reconsidered with each new oral drug regimen. ACE inhibitors were shown to reduce mortality in chronic heart failure, nevertheless a 30–40 % 4-year mortality remains. Moreover, there is evidence from recent trials that β-blockers combined with ACE inhibitors reduce mortality further by about 35 %, but patients in endstage heart failure on ACE inhibitors may pose a difficult problem for *de novo* β-blocker therapy. In contrast, with hospital-based intravenous support, haemodynamic stabilization of these patients may be achieved and maintained after discharge providing the opportunity to restructure oral medications, including *de novo* β-blocker titration [55–57].

Summary

The capability for carefully manipulating and combining intravenous PGE1 infusions with inotropic support with dobutamine has improved our ability to manage previously refractory transplant candidates. Such patients can be bridged to HTx at home with in-dwelling central venous catheters and portable automatic pumps. To assess the prognosis in this population, plasma levels of big endothelin which accumulates in the circulation of patients with high filling pressures can be used to single out those who are most in need of emergency transplantation.

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