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*CASE STUDY*

# Epoprostenol therapy for primary pulmonary hypertension after rejection of a single donor lung

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*Epoprostenol therapy for primary pulmonary hypertension after rejection of a single donor lung. R.J. Roeleveld, A. Vonk Noordegraaf, W. van der Bij, P.E. Postmus, A. Boonstra. ©ERS Journals Ltd 2003.*

**ABSTRACT: Before prostacyclins became available, lung or heart/lung transplantation was the only effective treatment for patients with primary pulmonary hypertension (PPH) who deteriorated under supportive medical treatment. Unfortunately, acute and chronic rejections occur in a large number of cases, limiting the average survival to 4.5 yrs.**

**A female patient, age 35 yrs, was diagnosed with PPH and underwent single lung transplantation. Despite aggressive immunosuppressive therapy, the patient had several episodes of acute rejection. Eventually, chronic rejection with bronchiolitis obliterans developed. After 5 yrs, the donor lung was no longer functional. The patient was in New York Heart Association (NYHA) class 4, had a 6-min walking distance of 50 m and a resting arterial oxygen tension ($P_{a,O_2}$) of 9.8 kPa (74 mmHg) when using 3 L·min$^{-1}$ of oxygen.**

**Epoprostenol treatment was started and the patient showed remarkable improvement. After 17 months the patient was NYHA class 2, walked 503 m in 6 min and had a resting $P_{a,O_2}$ of 10.9 kPa (82 mmHg) without supplemental oxygen.**

**In this patient, treatment with epoprostenol was effective after rejection of a single donor lung transplanted for primary pulmonary hypertension.**

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Primary pulmonary hypertension (PPH) is a rare, progressive disease with poor prognosis. Until only a few years ago, treatment consisted of supportive care, calcium antagonists and lung transplantation (LTx). However, transplant dysfunction because of rejection remains a major complication. For transplantations performed between 1991 and 1995 in the Netherlands for pulmonary hypertension, 2-yr survival is limited to ~50% [1, 2].

Over the last few years, treatment of PPH with prostacyclins has proven effective [3]. Initially considered as a bridge to transplantation, it is now thought that prostacyclins enable postponing of transplantation for a longer period of time, possibly even indefinitely [4]. This case report describes the course of a patient who underwent single LTx for PPH at the time when prostacyclins were not available for long-term treatment.

## Case report

A 35-yr-old female was diagnosed with pulmonary hypertension in late 1993. Secondary pulmonary hypertension was ruled out using laboratory and pulmonary function tests, high-resolution computed tomography, ventilation-perfusion scintigraphy and echocardiography. Although the patient had taken an undocumented dose of dexfenfluramine as a teenager, the final diagnosis was PPH. In 1995, further investigation was carried out, including acute vasodilator testing. During this test, the pulmonary artery pressure (PAP) decreased from 95/35/68 mmHg to 80/28/48 mmHg (-29%) after increasing doses of epoprostenol. There was no beneficial response on high levels of oxygen. Because of the diagnosis of PPH and subsequent deterioration of the patient's condition under supportive treatment with oxygen, oral anticoagulants and digoxin, the patient was listed for LTx.

At that time, only single LTx was performed for PPH in the Netherlands. Within a year after listing, an uncomplicated transplantation of the right lung was performed. Postoperative PAP was 36/11/19 mmHg. Ventilation-perfusion scintigraphy revealed an equal distribution of ventilation over both lungs, but 89% of the blood flow passed through the transplanted lung.

Immunosuppressive therapy consisted of antithymocyte globulins for induction, and corticosteroids, cyclosporin and azathioprine as maintenance therapy. Nevertheless, very frequent episodes of acute rejection occurred. Within 8 months after transplantation, the first signs of bronchiolitis obliterans were found in an open-lung biopsy. More aggressive immunosuppression with corticosteroids, tacrolimus and mycophenolate mofetil resulted in reduction of the frequency of acute rejections, but failed to halt the progression of bronchiolitis obliterans. Four and a half years after transplantation all functionality of the transplanted

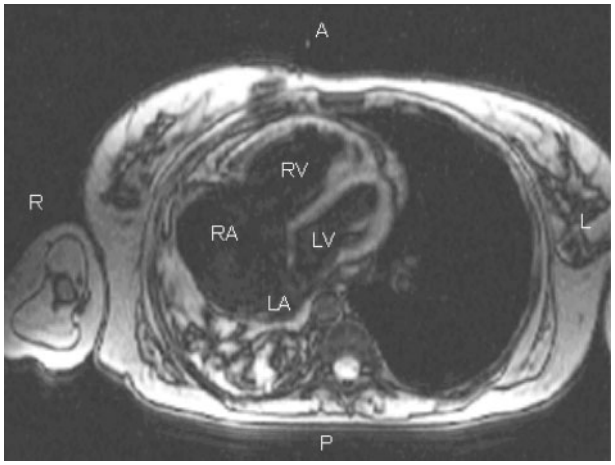


Fig. 1. – Chest magnetic resonance imaging (MRI) after donor lung rejection, transverse plane. RV: right ventricle; RA: right atrium; LV: left ventricle; LA: left atrium. The right hemithorax is filled with the remains of the transplanted lung and the heart. Note the severe enlargement of the RA and RV. Although not clearly visible on this image, the atrial septum was intact. The image was acquired with a black-blood prepared 2-dimensional turbo gradient echo pulse sequence. By using electrocardiogram triggering, the timing of image acquisition was adjusted during mid- to end-diastole of the cardiac cycle [5].

lung had been lost. Neither ventilation nor perfusion were detectable over the lung. Chest imaging showed remains of the donor lung and rightward shift of the heart (fig. 1).

At that time, the patient was severely dyspnoeic at rest, in New York Heart Association (NYHA) functional class 4 and had a 6-min walking distance of 50 m. Blood gas analysis revealed a resting arterial oxygen tension ($P_{a,O_2}$) of 9.8 kPa (74 mmHg) when using 3 L·min$^{-1}$ of oxygen. Retransplantation was considered. However, in the time that had passed since transplantation, epoprostenol had been registered in the Netherlands for use in PPH.

At right heart catheterisation, a PAP of 111/36/61 mmHg was found without any acute response on epoprostenol (table 1). Long-term epoprostenol therapy was started with an initial dose of 4.7 ng·kg$^{-1}$·min$^{-1}$ (500 mcg·24 h$^{-1}$), followed by an average monthly increase of 1 ng·kg$^{-1}$·min$^{-1}$. Within a month, the patient was less dyspnoeic and the 6 MWD had increased from 50 to 325 m. After 3 months, supplemental oxygen was discontinued, without negative effect on the exercise capacity. In the following months, the 6 MWD remained stable at ~350 m, but eventually increased to 503 m (fig. 2). Blood gas analysis showed a $P_{a,O_2}$ of 10.9 kPa (82 mmHg) without supplemental oxygen after 17 months of epoprostenol therapy. The patient is now classified as NYHA functional class 2 and generally feeling well. No right heart catheterisation was performed during the follow-up period, considering the fact that the findings would not affect the therapy in any way.

Table 1. – Haemodynamic measurements before transplantation (BT), after complete donor lung rejection (LR) and after 17 months of epoprostenol therapy (ET)

| Haemodynamic measurements | BT | LR | ET |
|---|---|---|---|
| PAP mmHg | 95/35/68 | 111/36/61 | |
| Lowest PAP$^{\#}$ mmHg | 80/28/48 | 105/27/58 | |
| Cardiac output L·min$^{-1}$ | 4.6$^{\P}$ | 2.4$^{+}$ | 3.5$^{+}$ |
| Stroke volume mL | 61$^{\P}$ | 31$^{+}$ | 46$^{+}$ |
| TPVR dyne·s·cm$^{-5}$ | 1182 | 2033 | |

PAP: pulmonary artery pressure; TPVR: total pulmonary vascular resistance. $^{\#}$: during reversibility testing; $^{\P}$: measured by catheterisation; $^{+}$: measured by magnetic resonance imaging velocity mapping.

## Discussion

Findings at the histological examination of the explanted right lung were consistent with the diagnosis of PPH, stage IV–V: intima proliferation, media hypertrophy and plexiform lesions were seen.

According to present standards, this patient should have been considered reversible at the vasodilator test before transplantation, as the decrease in PAP was >20%. The decision to list this patient for LTx immediately, without attempting treatment with calcium-channel blockers first, was not fully justified. Lack of experience with this rare disease and perhaps some confusion due to the difference in response on oxygen and epoprostenol may well have lead to this decision. The rapid deterioration under supportive care alone made listing for LTx a logical choice at that time.

Whether single or bilateral LTx is most beneficial for patients with PPH in general remains uncertain. Although some authors have noted that bilateral LTx has a somewhat better survival [6] and single LTx may result in significant ventilation/perfusion mismatches [7], single LTx is a well accepted modality [8–9]. More than 5 yrs after transplantation, chest imaging of the patient showed a fully sclerotic, collapsed donor lung, as a result of ongoing bronchiolitis obliterans and transplant vasculopathy. The patients survival on a prostacyclin-treated native lung enabled the development of a severe stage of bronchiolitis obliterans in

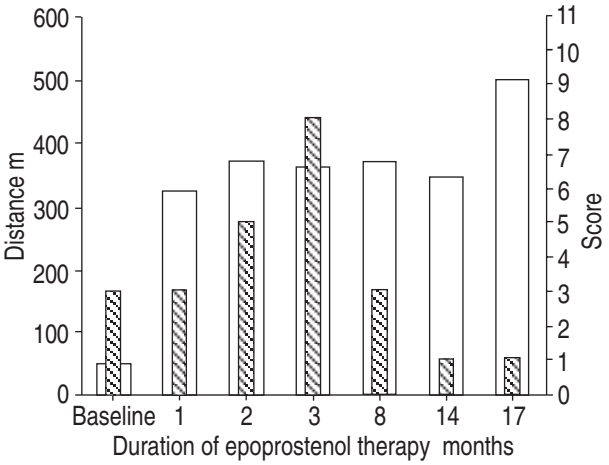


Fig. 2. – Six-min walk test results (□) and Borg dyspnoea score (▨).

the transplant, which is unusual and obviously not compatible with life.

To the best of the authors' knowledge, no literature was available on the use of epoprostenol after LTx and subsequent rejection. The decision to start this therapy rather than listing for retransplantation was therefore based upon the general treatment algorithm for PPH patients [10] as follows: 1) no response during vasodilator testing, 2) NYHA functional class III or IV, and 3) no listing for transplantation unless epoprostenol therapy fails. This case demonstrates that epoprostenol treatment can be effective after single LTx and subsequent rejection. Furthermore, it is demonstrated that patients who are initially not treated with prostacyclins, can still benefit from that form of treatment in a later stage of their disease, even with only one lung with severe PPH.

With hindsight, several therapeutic decisions concerning this patient have been controversial at best. The use of single lung transplantation as an unexpected bridge to epoprostenol treatment did however result in a long survival (>8 yrs after the diagnosis) and a good exercise capacity.

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