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CAUTIOUS USE OF EPOPROSTENOL THERAPY IS A SAFE BRIDGE TO LUNG TRANSPLANTATION IN PULMONARY VENO-OCCLUSIVE DISEASE

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ABSTRACT

Pulmonary veno-occlusive disease (PVOD) carries a poor prognosis and lung transplantation is the only curative treatment. In PVOD, epoprostenol therapy is controversial as this condition may be refractory to specific therapy with an increased risk of pulmonary edema.

We retrospectively reviewed clinical, functional and hemodynamic data of 12 patients with PVOD (10 with histological confirmation) treated with continuous intravenous epoprostenol and priority listed for lung transplantation after January 1st, 2003.

All PVOD patients had severe clinical, functional and hemodynamic impairment at presentation. Epoprostenol was used at low dose ranges with slow dose increases and high dose diuretics. Only one patient developed mild reversible pulmonary edema. After 3-4 months, improvements were seen in NYHA functional class (class IV to III in 7 patients), cardiac index (1.99±0.68 to 2.94±0.89 L/min/m²) and indexed pulmonary vascular resistance (28.4±8.4 to 17±5.2 U/m²) (all $p<0.01$). A non-significant improvement in 6-minute walk distance was also observed (+41m, $p=0.11$). Two patients died, one patient is alive on the transplantation waiting list and nine patients were transplanted.

Cautious use of continuous intravenous epoprostenol improved clinical and hemodynamic parameters in PVOD patients at 3-4 months without commonly causing pulmonary edema, and may be a useful bridge to urgent lung transplantation.

Key-words (MESH database): Epoprostenol, Lung transplantation, Pulmonary arterial hypertension, Prostacyclin, Pulmonary edema, Pulmonary veno-occlusive disease

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe condition characterized by elevated pulmonary artery pressure and normal pulmonary capillary wedge pressure (PCWP), leading to right heart failure and death (1-3). Pulmonary veno-occlusive disease (PVOD) is a sub-group of pulmonary hypertension with clinical similarities with PAH defined by specific pathological changes of the small pulmonary veins, and it represents 5 to 10% of histological forms of cases initially considered as idiopathic PAH (4-7). A definitive diagnosis of PVOD has been considered to require histological examination of lung samples showing extensive and diffuse occlusion of pulmonary veins by fibrous tissue and intimal thickening involving preferentially venules and small veins in lobular septa (8-10). We have recently demonstrated that a non-invasive approach can be helpful to screen for PVOD patients (6). Following this, we have used a non-invasive approach to screen patients with a high clinical suspicion of PVOD with methods including high-resolution computed tomography of the chest, diffusing lung capacity of carbon monoxide and bronchoalveolar lavage (6, 11, 12).

PVOD patients have a very poor prognosis and the recommended treatment is lung transplantation (4-7). In these patients with severe pulmonary vascular disease, the waiting time for transplantation may exceed their expected survival. While specific PAH therapies such as intravenous prostacyclin have established efficacy in treatment of PAH (3, 13), benefits of these treatments in patients with PVOD are unclear, as these patients may be refractory to PAH specific therapy and may even deteriorate with it. Recently, Montani et al reported the occurrence of pulmonary edema with different specific PAH therapies (epoprostenol, bosentan, calcium channel-blocker) suggesting that pulmonary edema is not due to a therapeutic class effect but may occur with all specific PAH therapies (6). In this series nearly half of the PVOD patients treated with epoprostenol developed pulmonary edema (6). However, continuous intravenous epoprostenol is considered to be the most potent

therapy in severe PAH, combining pulmonary vasodilatory and antiproliferative effects and it has been shown to improve exercise capacity, hemodynamics and survival of idiopathic PAH patients (3, 14-18). Epoprostenol has been proposed as a bridging therapy in various severe pulmonary vascular diseases including various PAH variants and non-operable chronic thromboembolic pulmonary hypertension patients awaiting lung transplantation (3, 14-19). In PVOD, isolated case reports suggested that cautious use of epoprostenol may be helpful to stabilise the condition (4, 10, 20). With the improved identification of this rare subgroup of PAH, we hypothesized that continuous intravenous epoprostenol, when used in a cautious manner, could improve hemodynamic and functional status of severe PVOD patients waiting for lung transplantation and may be used as a bridge to lung transplantation. The aim of the present study was to report our experience on the use of epoprostenol in PVOD patients awaiting lung transplantation.

METHODS

Patients

We retrospectively reviewed data from patients referred to the French Reference Center for Pulmonary Hypertension (Université Paris-Sud 11, Hôpital Antoine Béclère, Clamart, France) with confirmed or highly probable PVOD, treated with continuous intravenous epoprostenol and listed for lung transplantation after January 1st, 2003. Two patients were reported in a previous article (6). Diagnosis of PVOD was considered as confirmed when histological proof of veno-occlusive disease (biopsy, post-mortem or lungs obtained after lung transplantation) was available or when pulmonary edema had occurred with specific PAH therapy. The diagnosis of PVOD was considered as very highly probable if patients fulfil the characteristics we have previously described (6): precapillary pulmonary hypertension confirmed by right heart catheterisation, presence of 2 or more radiological abnormalities on high-resolution computed tomography of the chest (including lymph node enlargement, centrilobular ground-glass opacities and septal lines), low diffusing lung capacity of carbon monoxide (DLCO) and occult alveolar hemorrhage. Pulmonary hypertension occurring in patients associated with other conditions (connective tissue diseases, human immunodeficiency virus infection, portal hypertension, congenital heart diseases and chronic respiratory diseases) were excluded from the study. All clinical characteristics at diagnosis and follow-up were stored in the Registry of the French Network of Pulmonary Hypertension. This registry was set up in agreement with French bioethics laws (French Commission Nationale de l'Informatique et des Libertés) and all patients gave their informed consent (21).

Pathology

Hematoxylin-Eosin-Safran staining was used to characterize pulmonary vascular abnormalities. The pathologic hallmark of PVOD was defined as an extensive and diffuse

obstruction of pulmonary veins and venules by intimal fibrosis, cellular proliferation and muscularization (8, 22, 23). When available, occult alveolar hemorrhage was assessed by Golde score on bronchoalveolar lavage performed during bronchoscopy, and an alveolar hemorrhage was defined by a Golde score >100 (12). Histological confirmation was obtained from explanted lung in 9 patients (75%) and by autopsy in 1 patients (8%), one patient died without post-mortem analysis and one patient was still waiting for lung transplantation on December 1st, 2008.

Hemodynamic measurements

Precapillary pulmonary hypertension was defined as mPAP >25 mmHg with a normal PCWP <15 mmHg. mPAP, PCWP, right atrial pressure (RAP) and mixed venous oxygen saturation (SvO2) were recorded. Cardiac output (CO) was measured by the standard thermodilution technique. The cardiac index (CI) was calculated as the CO divided by the body surface area and systolic index as the CI divided by heart rate. The indexed pulmonary vascular resistance (PVRi) were calculated as (mPAP-PCWP)/CI, expressed in Wood Units/m². Baseline hemodynamic data and response to short-term vasodilator nitric oxide (NO) were performed for all subjects. A NO challenge (10 ppm for 5-10 minutes) was used and a positive acute response was defined as a decrease in mPAP of more than 10 mmHg compared to the baseline mPAP to a mPAP lower than 40 mmHg and a normal or increased CO, as previously described (24).

Clinical and functional assessment

Routine evaluation at baseline included medical history and physical examination. Age at diagnosis, smoking habits, and clinical status assessed by modified New-York Heart Association (NYHA) functional class (2, 3) were recorded at diagnosis. A non-encouraged 6-

minute walk test according to the American Thoracic Society recommendations (25) was performed. The 6-minute walk distance (6MWD) and the lowest pulse arterial oxygen saturation (minimal SpO2) were both recorded (26, 27). Arterial blood gases and lung function tests were performed: partial pressure of arterial oxygen (PaO_2) and DLCO were recorded.

Epoprostenol therapy

Continuous intravenous epoprostenol was initiated in PVOD patients eligible for lung transplantation in NYHA functional class III or IV with severely impaired hemodynamics. All patients received continuous intravenous epoprostenol initiated during hospitalisation. At the time of epoprostenol initiation, non-specific therapy including warfarin, diuretics, dobutamine and oxygen if needed and associated specific PAH therapies were recorded. The occurrence of pulmonary edema and need to increase diuretics after initiation of continuous epoprostenol were reported. Management of epoprostenol therapy was also recorded, including the time between diagnosis and initiation, the maximum dose, the time to reach the maximal dose and the length of epoprostenol therapy. We recorded data regarding NYHA functional class, hemodynamics, pulmonary function tests and 6-minute walk distance from evaluation at 3-4 months and at 9-12 months after initiation of epoprostenol.

Lung transplantation

All the patients were listed for lung transplantation at the time of epoprostenol initiation. According to current national guidelines for pulmonary or cardiopulmonary transplantation, PVOD patients could be listed for an urgent priority transplantation procedure if they were at high risk of short-term mortality, as defined by persistent clinical and hemodynamic instability requiring continuous vasoactive drug infusion (dobutamine and norepinephrine) in

intensive care unit. The time between listing for lung transplantation and transplantation or death, the type of lung transplantation (heart and lungs or double lungs) and mortality at day 28 post-transplantation were recorded.

Statistical analysis

Statistical analysis was performed using Stat view version 5.0 (Abacus Concepts Inc., Berkley, CA, USA). Data are presented as mean +/- standard deviation (STD) unless stated otherwise. Comparisons of hemodynamic data between baseline evaluation and 3-4 months later were assessed by paired t-tests or by non-parametric tests if needed. Survival analysis were calculated using the Kaplan-Meier method. For patients who were transplanted before the hemodynamic evaluation at 3-4 months, we used the last evaluation of NYHA functional class and 6-MWD, and the hemodynamic characteristics on the day of lung transplantation. For the only patient who died before hemodynamic evaluation, we used the worse value of 6–MWD and hemodynamic characteristics of the cohort in the statistical analysis.

RESULTS

Baseline characteristics

Between January 1st, 2003 and December 1st, 2008, twelve PVOD patients treated with continuous intravenous epoprostenol and listed for lung transplantation were identified. Eleven patients (91.7%) had a confirmed diagnosis of PVOD: 10 patients had histologically confirmed PVOD on explanted lungs and one patient with characteristics of PVOD (3 radiological abnormalities, DLCO of 43%) developed pulmonary edema with calcium channel blocker therapy. The last patient was waiting for lung transplantation on December 1st, 2008 and had highly probable PVOD with precapillary pulmonary hypertension associated with

two radiological abnormalities (centrilobular ground-glass opacities and septal lines), DLCO of 25% and an occult alveolar hemorrhage on bronchoalveolar lavage.

Demographic, clinical, functional and hemodynamic characteristics at diagnosis of the PVOD patients are presented in **Table 1**. As previously described (4-7), there was no female predominance and tobacco exposure was common in this patient population. One patient had a family history of PVOD (a sister with histologically confirmed PVOD). This patient and 7 other PVOD patients without family history were screened for the *BMPR2* mutation and interestingly, a *BMPR2* mutation was found in a patient without a known family history of PAH or PVOD. At the time of diagnosis, most of the patients were in NYHA functional class III (class II, n=1; class III, n=8 and class IV, n=3) with severe hemodynamic impairment (high PVRi, low CI and SvO2 and normal PWCP) (**Table 1**). PVOD patients typically had low resting PaO2, marked oxygen desaturation during 6-MWD, very low DLCO and possible occult alveolar hemorrhage (n=3, 33.3%) (4-7, 12). Furthermore, at least 2 classical radiological abnormalities, including lymph node enlargement, centrilobular ground-glass opacities and septal lines, were found in all patients. The patient who responded favourably to acute vasodilator testing (NO) was the only patient in functional class II at the time of diagnosis. This patient developed pulmonary edema and clinical deterioration with calcium channel blocker therapy prior to cautious initiation of continuous intravenous epoprostenol. Despite the fact that only one patient was an acute NO responder according to the current definition (24), an element of acute vasoreactivity to NO was relatively frequent with a mean change of mPAP during NO testing of 6±4 mmHg ($p<0.001$).

Epoprostenol therapy

NYHA functional class, 6-MWD and hemodynamic characteristics of PVOD patients at the time of initiation of epoprostenol are presented in **table 2**. At this time, all PVOD patients

were in NYHA functional class III (n=4) or IV (n=8) with severe impaired hemodynamics (CI 1.99±0.68 L/min/m² and PVRi 28.4±8.4 U/m²). All 12 patients were treated by continuous intravenous epoprostenol within one year of diagnosis (median time between diagnosis and initiation of 68 days, range 1-358) (**Table 2**). All were listed for lung transplantation and epoprostenol was used as a bridge to transplantation. The median value of the maximal dose of epoprostenol reached in these patients was 13 ng/kg/min (range 5-22). This dose was obtained with a slow increase in dose titration (median time to reach maximal dose 150 days, range 5-1065). At the time of initiation of epoprostenol, all PVOD patients received non-specific PAH therapies including diuretics, anticoagulation and oxygen in 100%, 91.7% and 66.7% respectively. All patients received diuretics: furosemide was used in all patients with additional spironolactone in 8 patients (66.7%). Because of the severity of the disease, 3 patients were hospitalised in the intensive care unit and received management for associated right ventricular failure with dobutamine at the time of initiation of epoprostenol.

In terms of combination therapy, 8 patients (66.7%) received the dual endothelin-receptor antagonist bosentan at the time of initiation of prostacyclin: 7 patients received epoprostenol as an add-on therapy after insufficient response to first-line bosentan therapy and epoprostenol and bosentan were initiated simultaneously in one patient.

Side effects and risk of pulmonary edema with epoprostenol therapy in PVOD

Common side effects were observed in all patients including one or more of the following events: flushing, headaches, nausea, vomiting, diarrhoea and abdominal discomfort. Neither the 3 patients with confirmed occult alveolar hemorrhage nor the remaining 9 patients developed hemoptysis. Two episodes of central line sepsis occurred in one patient (63 and 195 days after initation of epoprostenol) with an incidence of catheter-related infections requiring change of central line of 0.64 per 1000 catheter days. No further deterioration in gas

exchange was evidenced after initiation or 3-4 months of epoprostenol therapy. Only one patient developed mild pulmonary edema which rapidly improved with an increase in diuretic therapy. An increase in diuretics was necessary in 4 patients (33.3%) because of the occurrence of lower limb edema (n=3) or an increase in radiological abnormalities (n=1). Interestingly, one patient had previously developed acute pulmonary edema 7 days after initiation of calcium channel blocker therapy indicated because of an acute NO response (**Table 1**). However, this patient did not develop pulmonary edema with a low dose of continuous epoprostenol infusion (epoprostenol 5ng/kg/days for 30 days).

Evolution of clinical, functional and hemodynamic parameters with epoprostenol

Evolution of clinical, functional and hemodynamic parameters of PVOD patients between 3 and 4 months following initiation of epoprostenol therapy or at the last evaluation before transplantation or death is presented in **table 2**.

NYHA functional class and 6-minute wqlk distance

Prior to initiation of epoprostenol, one third (n=4) of the patients was in NYHA functional class III and two third (n=8) were in class IV. After 3-4 months (n=8) or at the last evaluation before transplantation or death (n=4), NYHA functional was improved for most of the patients ($p<0.001$), but none of them improved to functional class I or II (**Figure 1**). Eleven patients were in NYHA functional class III and only one patient remained in class IV (**Figure 1**). Three patients still waiting for lung transplantation were evaluated between 9 and 12 months of epoprostenol therapy, these 3 patients remained stable in NYHA functional class III.

6-MWD was slightly improved from 281±162 [Min-Max 0-508] to 322±160 [Min-Max 0-469] but the difference does not reach statistical significance (+41m, p=0.11) (**Figure 2**).

Hemodynamic parameters

At 3-4 months, an improvement of hemodynamics was observed with a significant decrease of mPAP (p=0.05), PVRi (p<0.0001) and a significant increase of CI (p=0.002), systolic index (p=0.001) and SvO2 (p=0.01) (**Figure 3**). One patient developed reversible pulmonary edema with epoprostenol which was managed with titration of diuretic therapy. Interestingly, this patient had an overall hemodynamic improvement (PVRi from 23.9 to 16.9 UW/m^{-2}, CI from 1.84 to 2.54 l/m^{-2}). Evaluation of the 3 patients alive and not transplanted 6 months after initiation of epoprostenol, showed a trend to a return towards baseline with deterioration in the functional and hemodynamic improvements observed after 3-4 months (data not shown).

Epoprostenol as a bridge-therapy to lung transplantation

For all patients, listing for lung transplantation was proposed in the first year following initiation of epoprostenol (median 2.4 months, min-max 0-12). As of the 1st of December 2008, 9 out of 12 patients were transplanted, 2 died before lung transplantation at day 145 and 201 and 1 was still waiting for lung transplant at day 434 (**Table 4**). The median time between listing and lung transplantation was 49 days (1-357). In the 9 transplanted PVOD patients, 5 had a heart and lung transplantation and 4 had a double lung transplantation, all of whom were alive at day 28 after surgery (**Table 4**). Seven (58.3%) and 11 (91.7%) out of 12 patients had died or had been transplanted at 6 and 12 months following listing for lung transplantation, respectively. The time from diagnosis to death or lung transplantation is presented in **Figure 4A**.

In the 9 transplanted patients, 3 died at day 52, 74 and 79 after lung transplantation, respectively. Six were still alive after lung transplantation with a median follow-up of 447 days (min-max 80 - 930 days). The cumulative survival of PVOD patients benefiting from a

management strategy combining PAH basic therapy, intravenous epoprostenol and listing for lung transplantation is presented in **Figure 4B**. Such management was associated with a 1- and 2-year survival of 83% and 50%, respectively.

DISCUSSION

In this series of well characterized PVOD patients awaiting lung transplantation, continuous intravenous epoprostenol appeared to be safe when used with a slow increase in dosage and with high-dose diuretics and may improve functional and hemodynamic status at 3-4 months. Even if no long-term benefit was noted, epoprostenol may be considered as a potentiel bridge-therapy to lung transplantation in these severe patients.

First, we confirmed findings from the previous series where PVOD patients were characterized by low DLCO, radiological abnormalities, possible occult alveolar hemorrhage and a frequent association with tobacco exposure (4, 6, 11, 12). Interestingly, radiological abnormalities including centrilobular ground-glass opacities, septal lines and lymph node enlargement, were present in all these PVOD patients with severe disease, highlighting the sensitivity of these radiological characteristics to screen for PVOD patients (4, 6, 11, 12). As previously reported by Rabiller and colleagues in a different series of patients, 7/9 of our patients had a Golde score >20, including 2 with a Golde score >100 (12). This series confirmed that some PVOD patients may have an acute vasodilator response (24) and even an incomplete response to acute NO testing seems to be common. Interestingly, acute responders from the present series and our previous series (6) had a similar evolution marked by severe pulmonary edema occurring a few days after initiation of calcium channel blockers, further contraindicating their use in PVOD patients even when an acute NO response is present.

After 3-4 months of epoprostenol, we observed evidence of hemodynamic improvement with a significant decrease of PVRi (-38%) and a significant effect on systolic function with an

increase in CI (+48%) and systolic index (+45%). As observed in idiopathic PAH, epoprostenol had a predominant effect on cardiac function and pulmonary vascular resistance but a mild but significant decrease of mPAP was also seen. We observed a non-significant increase in 6-MWD (+41m, p=0.11) with a level of improvement lower than previously described in large cohorts of idiopathic PAH patients treated with intravenous epoprostenol in our center (+125m at 3 months) (18). One could suggest that the response observed at 3-4 months may be due to a selection bias with inclusion of only the survivors who can be listed for lung transplantation. However, this study included all PVOD patients who received epoprostenol and were listed for lung transplantation during the study period. During the same period, only 2 PVOD patients received epoprostenol without being listed for lung transplantation because of contraindications. In these 2 PVOD patients, functional and hemodynamic improvement was broadly similar to PVOD patients listed for lung transplantation (patient 1: PVRi -24%, 6-MWD +105m; patient 2: PVRi -27%, 6-MWD +50m). We can therefore conclude that the improvement observed was not due to a selection bias of survivors. Despite substantial hemodynamic improvements, the clinical response was less impressive, with no patients improving to NYHA functional class I or II, a clinical status considered as an accurate prognostic factor in idiopathic PAH patients treated by epoprostenol (18). Even though few data on long-term response were available, no further clinical and hemodynamic improvement seemed to be obtained after 6 months, also differing from reports in idiopathic PAH (15, 16, 18).

In canine models, it has been suggested that epoprostenol may have pulmonary venodilatory properties, however little is known in humans and particularly in PVOD patients (28, 29). Other agents such as sildenafil also have venodilating properties, and there are cases of clinical improvement on sildenafil monotherapy in PVOD patients (30, 31) or in combination with high-dose epoprostenol in one case (32). However, pulmonary edema may also occur in

sildenafil-treated PVOD (Montani et al, unpublished observation). In the present PVOD study, the doses of continuous intravenous epoprostenol administered may appear to be relatively low. However, the doses after 3 months are in fact similar to those reported by Sitbon et al 3 months after initiation of epoprostenol in idiopathic PAH (14+/-4 ng/kg/min, range 7-34) (18). Our study suggests that even a low dose of epoprostenol may improve hemodynamics in PVOD at 3 months. The absence of further improvement observed after 6 months may be due to tachyphylaxis, classically observed with intravenous epoprostenol use. In our experience, however, a further increase of the epoprostenol dose in PVOD patients who experienced a clinical deterioration was not followed by clinical improvement. Interestingly, more than half of the patients reported in this study received epoprostenol in combination with the dual endothelin antagonist bosentan without evidence of pulmonary edema, indicating that awareness and drug titration are key elements to prevent this life-threatening complication of PVOD.

A very low incidence of pulmonary edema was observed (only one mild reversible case was reported) compared to the data published in our previous series in which nearly half of the patients treated with epoprostenol developed pulmonary edema (6). This difference may be explained by the different periods of these two series, the second one being performed at a time with improved awareness of PVOD. The first series (6) was performed at a time when non-invasive screening for PVOD was not systematically used and for most patients, PVOD was not diagnosed until the occurrence of pulmonary edema or histological analysis after lung transplantation or post-mortem examination of the lungs. At that time, epoprostenol was used without specific caution, using the same protocol as for idiopathic PAH patients. This second series of PVOD patients used a non-invasive approach to screen for highly probable PVOD in whom epoprostenol was initiated. In this series, the time to reach the dose of 10 ng/Kg/min of epoprostenol was 10 to 15 days and initiation of epoprostenol was associated with high-dose

diuretics. The rate of epoprostenol up-titration was slower than in idiopathic PAH (5 days) and than in our previous series of PVOD patients (6). Interestingly, 5/11 PVOD patients developed pulmonary edema with epoprostenol (median dose 9 ng/Kg/min) in our previous series (6) as compared to 1/12 in this current cohort despite a higher median dose (13 ng/Kg/min). These data support the hypothesis that the method of screening of high-risk patients together, with the use of specific precautions such as slow rate of up-titration and the use of high-dose diuretics may limit the risk of pulmonary edema. Interestingly, no significativative deterioration of hypoxemia was observed in PVOD patients after 3-4 months of intravenous epoprostenol therapy. Last, the incidence of catheter-related infection in PVOD patients was similar to the incidence previously described in PAH patients receiving epoprostenol (33, 34), suggesting that this patient population was not more prone to develop sepsis on intravenous epoprostenol.

Because of clinical and hemodynamic improvement in PVOD patients without commonly causing pulmonary edema, cautious use of continuous intravenous epoprostenol might be helpful in the management of these patients as a bridge to lung transplantation. In this series, 11/12 the patients died or were transplanted within 12 months following listing for lung transplantation. Only two patients died while waiting for lung transplantation and 9 were transplanted with a median time between listing and lung transplantation of less than 2 months. This relatively short waiting time before lung transplantation is mainly explained by the recent availability in France of urgent priority lung and heart-lung transplantation, which certainly lead to earlier transplantation. Three patients died in the first 3 months after transplantation and the overall survival appears to be worse than reported in the UNOS registry. This may be explained at least in part by the severity of these patients who were listed for urgent lung transplantation because of hemodynamic instability. However, we cannot statistically compare these results with overall survival statistics in lung

transplantation due to the small number of patients in this series. Short-term and long-term survival after urgent transplantation in PVOD patients should be studied prospectively in future studies. We previously demonstrated that a multiple non-invasive approach including HRCT of the chest, pulmonary function tests (DLCO, PaO2 at rest, low spO2 during 6MWT) and bronchoalveolar lavage if possible, allowed to screen highly probable PVOD patients (6) and to propose a cautious use of intravenous epoprostenol. In our center, PVOD patients screened by a non invasive approach received PAH basic therapy, continuous intravenous epoprostenol and priority lung transplantation if eligible. This strategy of "best standard of care" allowed a survival of severe PVOD patients of 83% at 1 year and 50% at 2 years, that seemed to be higher than previously suggested in PVOD patients (4-7).

Furthermore, no specific complication was observed in these patients during or after lung transplantation, and all the transplanted patients were alive 28 days after surgery. However, we have previously demonstrated that even if baseline hemodynamic, NYHA and 6MWD parameters are similar to that observed in a series of PAH patients, PVOD patients have a worse outcome if not transplanted (4-6). Unlike idiopathic PAH in which epoprostenol may lead to sustained improvements in hemodynamics and survival for prolonged periods, epoprostenol was not a suitable alternative to transplantation in PVOD patients (35). Because of PVOD constant deterioration and poor prognosis, waiting for deterioration may be devastating for these patients and initiation of continuous intravenous epoprostenol should not delay lung transplantation (10). In our experience, when eligible, the patients with confirmed or a very highly probable diagnosis of PVOD should be listed for urgent lung transplantation concomitantly to the initiation of continuous intravenous epoprostenol. This study suggests the potential efficacy and the safety of this strategy for PVOD patients.

In conclusion, we have demonstrated that continuous intravenous epoprostenol may be efficient and safe in PVOD patients when used with specific precautions, including the use of high-dose diuretics and a slowly titrated increase in dose. However, although epoprostenol leads to an initial improvement, this is not sustained after 6 months, suggesting that it is most suited as a bridging therapy before lung transplantation in patients with PVOD.

REFERENCES

1. Rubin L. Primary pulmonary hypertension. N Engl J Med 1997;336:111-7.

2. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5S-12S.

3. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med 2004;351:1425-36.

4. Holcomb BW, Jr., Loyd JE, Ely EW, Johnson J, Robbins IM. Pulmonary veno-occlusive disease: a case series and new observations. Chest 2000;118:1671-9.

5. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. Am J Respir Crit Care Med 2000;162:1964-73.

6. Montani D, Achouh L, Dorfmuller P, Le Pavec J, Sztrymf B, Tcherakian C, Rabiller A, Haque R, Sitbon O, Jaïs X, Dartevelle P, Maitre S, Capron F, Musset D, Simonneau G, Humbert M. Pulmonary veno-occlusive disease: Clinical, functional, radiologic, hemodynamic characteristics and outcome of 24 cases confirmed by histology. Medicine (Baltimore) 2008;87:220-33.

7. Montani D, Price LC, Dorfmuller P, Achouh L, Jais X, Yaici A, Sitbon O, Musset D, Simonneau G, Humbert M. Pulmonary veno-occlusive disease. Eur Respir J 2009;33:189-200.

8. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, Reid LM, Tuder RM. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 2004;43:25S-32S.

9. Lantuejoul S, Sheppard MN, Corrin B, Burke MM, Nicholson AG. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: a clinicopathologic study of 35 cases. Am J Surg Pathol 2006;30:850-7.

10. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Thorax 2008;63 Suppl 2:ii1-ii41.

11. Resten A, Maitre S, Humbert M, Rabiller A, Sitbon O, Capron F, Simonneau G, Musset D. Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. AJR Am J Roentgenol 2004;183:65-70.

12. Rabiller A, Jais X, Hamid A, Resten A, Parent F, Haque R, Capron F, Sitbon O, Simonneau G, Humbert M. Occult alveolar haemorrhage in pulmonary veno-occlusive disease. Eur Respir J 2006;27:108-13.

13. Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J 2008;31:891-901.

14. Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE. Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. Circulation 1982;66:334-8.

15. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296-302.

16. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 1998;338:273-7.

17. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann XJ, Georgiou D, Mandayam S, Ginzton LE, Brundage BH. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am Coll Cardiol 1997;30:343-9.

18. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau

G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-8.

19. Cabrol S, Souza R, Jais X, Fadel E, Ali RH, Humbert M, Dartevelle P, Simonneau G, Sitbon O. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant 2007;26:357-62.

20. Okumura H, Nagaya N, Kyotani S, Sakamaki F, Nakanishi N, Fukuhara S, Yutani C. Effects of continuous IV prostacyclin in a patient with pulmonary veno-occlusive disease. Chest 2002;122:1096-8.

21. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023-30.

22. Chazova I, Robbins I, Loyd J, Newman J, Tapson V, Zhdaov V, Meyrick B. Venous and arterial changes in pulmonary veno-occlusive disease, mitral stenosis and fibrosing mediastinitis. Eur Respir J 2000;15:116-22.

23. Dorfmuller P, Humbert M, Perros F, Sanchez O, Simonneau G, Muller KM, Capron F. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. Hum Pathol 2007;38:893-902.

24. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.

25. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.

26. Provencher S, Chemla D, Herve P, Sitbon O, Humbert M, Simonneau G. Heart rate

responses during the 6-minute walk test in pulmonary arterial hypertension. Eur Respir J 2006;27:114-20.

27. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 2001;17:647-52.

28. Davis LL, deBoisblanc BP, Glynn CE, Ramirez C, Summer WR. Effect of prostacyclin on microvascular pressures in a patient with pulmonary veno-occlusive disease. Chest 1995;108:1754-6.

29. Greenberg S. Effect of prostacyclin and 9a, 11a-epoxymethanoprostaglandin H2 on calcium and magnesium fluxes and tension development in canine intralobar pulmonary arteries and veins. J Pharmacol Exp Ther 1981;219:326-37.

30. Barreto AC, Franchi SM, Castro CR, Lopes AA. One-year follow-up of the effects of sildenafil on pulmonary arterial hypertension and veno-occlusive disease. Braz J Med Biol Res 2005;38:185-95.

31. Creagh-Brown BC, Nicholson AG, Showkathali R, Gibbs JS, Howard LS. Pulmonary veno-occlusive disease presenting with recurrent pulmonary oedema and the use of nitric oxide to predict response to sildenafil. Thorax 2008;63:933-4.

32. Kuroda T, Hirota H, Masaki M, Sugiyama S, Oshima Y, Terai K, Ito A, Yamauchi-Takihara K. Sildenafil as adjunct therapy to high-dose epoprostenol in a patient with pulmonary veno-occlusive disease. Heart Lung Circ 2006;15:139-42.

33. Oudiz RJ, Widlitz A, Beckmann XJ, Camanga D, Alfie J, Brundage BH, Barst RJ. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest 2004;126:90-4.

34. Sitbon O, Humbert M, Simonneau G. Primary pulmonary hypertension: Current therapy. Prog Cardiovasc Dis 2002;45:115-28.

35. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 1994;121:409-15.

TABLE 1. CHARACTERISTICS OF PVOD PATIENTS AT DIAGNOSIS OF PRECAPILLARY PULMONARY HYPERTENSION (n=12)

	At diagnosis
Sex : Male / Female	7 / 5
Age at diagnosis, yrs	41 ± 12
Tobacco exposure, pack year	16 ± 17.3
NYHA class at diagnosis Class II Class III Class IV	 1 (8.3%) 8 (66.7%) 3 (25%)
Six-minute walk test Distance, m Nadir SpO2, %	 353 ± 103 83 ± 6
PaO_2 (mmHg)	66 ± 8
$PaCO_2$ (mmHg)	29 ± 4
DLCO (%pred)	34 ± 14
mPAP (mmHg)	56 ± 10
RAP (mmHg)	8 ± 6
PCWP (mmHg)	7 ± 3
CI (L/min/m²)	2.40 ± 0.72
SI (mL/m²)	26 ± 5
PVRi (U/m²)	23.3 ± 10.6
SvO2 (%)	61 ± 12
Acute NO Responders	1 (8.3%)
Delta mPAP with NO, %	10 ± 7
Number of patients with ≥2 radiological abnormalities*	12 (100%)
Occult alveolar hemorrhage†	3/9 (33.3%)

SpO2= pulse arterial oxygen saturation, DLCO/VA= diffusing lung capacity of carbon monoxide /alveolar volume, PaO2=arterial partial pressure of oxygen, mPAP= mean pulmonary artery pressure, RAP= right atrial pressure, PCWP= pulmonary capillary wedge pressure, CI= cardiac index SI= Systolic index, PVRi= Pulmonary vascular resistance index, SvO2= mixed venous oxygen saturation, NO= nitric oxide.

* Radiological abnormalities on high-resolution computed tomography of the chest include lymph node enlargement, centrilobular ground-glass opacities and septal lines.

† defined by Golde score >100.

TABLE 2: CLINICAL, FUNCTIONAL AND HEMODYNAMIC PARAMETERS BEFORE INTIATION OF EPOPROSTENOL AND AFTER 3-4 MONTHS (n=12).

	Before initiation of epoprostenol	**Evaluation after 3-4 months**	**P value**
NYHA functional class Class III Class IV	 4 8	 11 1	 <0.01
Six-minute walk distance, m	281 ± 162	322 ± 160	0.11
Hemodynamic characteristics			
mPAP (mmHg)	58 ± 8	53 ± 9	0.05
RAP (mmHg)	9 ± 6	8 ± 5	0.64
PCWP (mmHg)	6 ± 3	6 ± 3	0.48
CI (L/min/m²)	1.99 ± 0.68	2.94 ± 0.89	0.002
SI (mL/m²)	22.2 ± 5.7	33.2 ± 9.7	0.001
PVRi (U/m²)	28.4 ± 8.4	17 ± 5.2	<0.0001
SvO2 (%)	56 ± 8	64 ± 12	0.01

SpO2= pulse arterial oxygen saturation, mPAP= mean pulmonary artery pressure, RAP= right atrial pressure, PCWP= pulmonary capillary wedge pressure, CI= cardiac index, PVRi= Pulmonary vascular resistance index, SvO2= mixed venous oxygen saturation.

Results are expressed as Mean ± STD

TABLE 3. CHARACTERISTICS AND SIDE-EFFECTS OF 3-4 MONTHS OF INTRAVENOUS EPOPROSTENOL THERAPY IN PVOD (n=12)

Time between diagnosis and initiation, *days*	68 (1-358)
Maximal Dose, *ng/Kg/min*	13 (5-22)
Time to reach maximal dose, *days*	150 (5-1065)
Length of treatment with epoprostenol, *days*	210 (18 - 1106)
Associated therapy at the time of initiation: Oxygen Anticoagulation Diuretics: - Furosemide, n daily dose (mg) - Spironolactone, n daily dose (mg) Dobutamine Bosentan	 8 (66.7%) 11 (91.7%) 12 (100%) 80 (40-250) 8 (66.7%) 50 (25-75) 3 (25%) 8 (66.7%)
Need to increase diuretics	4 (33.3%)
Pulmonary edema with epoprostenol	1 (8.3%)
Need to initiate or increase oxygen therapy	0

Data are presented as Median (range min-max)

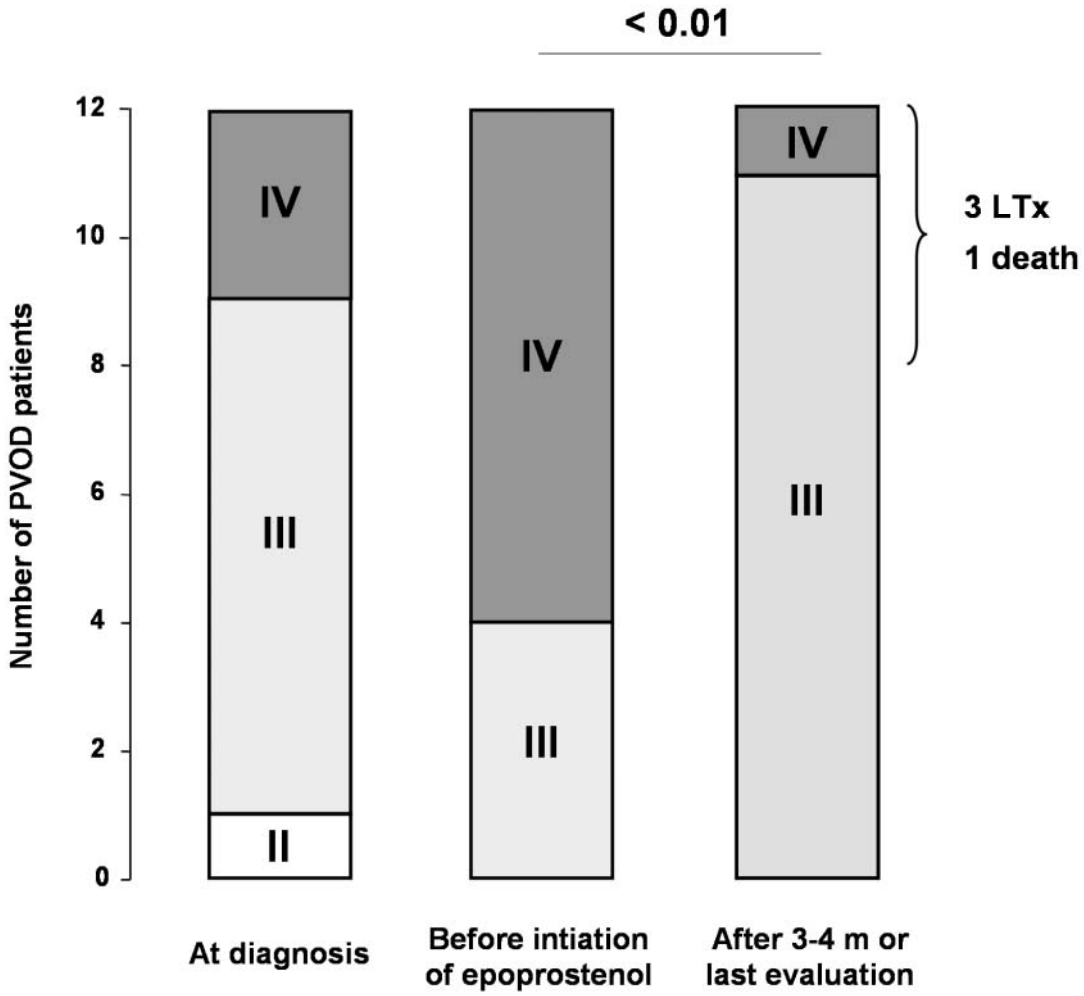
TABLE 4: LUNG TRANSPLANTATION OF PVOD PATIENTS WITH BRIDGE-THERAPY BY EPOPROSTENOL (n=12).

	Diagnosis of PVOD	Evolution	Time between inscription and LTx (days)	Type of LTx	Alive at day 28 after LTx	Evolution at the 1st December 2008
1	Pulmonary edema with CCB	Death 201 d after inscription	-	-	-	-
2	Explanted lungs	Lung transplantation	251	Heart Lung	Yes	death 52 d after LTx
3	Post-mortem	Death 145 d after inscription	-	-	-	-
4	Explanted lungs	Lung transplantation	43	Double Lung	Yes	alive at 930 d
5	Explanted lungs	Lung transplantation	173	Double Lung	Yes	death 79 d after LTx
6	Explanted lungs	Lung transplantation	357	Heart Lung	Yes	alive at 615 d
7	Explanted lungs	Lung transplantation	18	Heart Lung	Yes	alive at 826 d
8	Multiple approach screening	still waiting for lung transplant at day 464				
9	Explanted lungs	Lung transplantation	49	Double Lung	Yes	alive at 279 d
10	Explanted lungs	Lung transplantation	227	Double Lung	Yes	alive at 80 d
11	Explanted lungs	Lung transplantation	42	Heart Lung	Yes	alive at 235 d
12	Explanted lungs	Lung transplantation	1	Heart Lung	Yes	death 74 d after LTx

LEGENDS

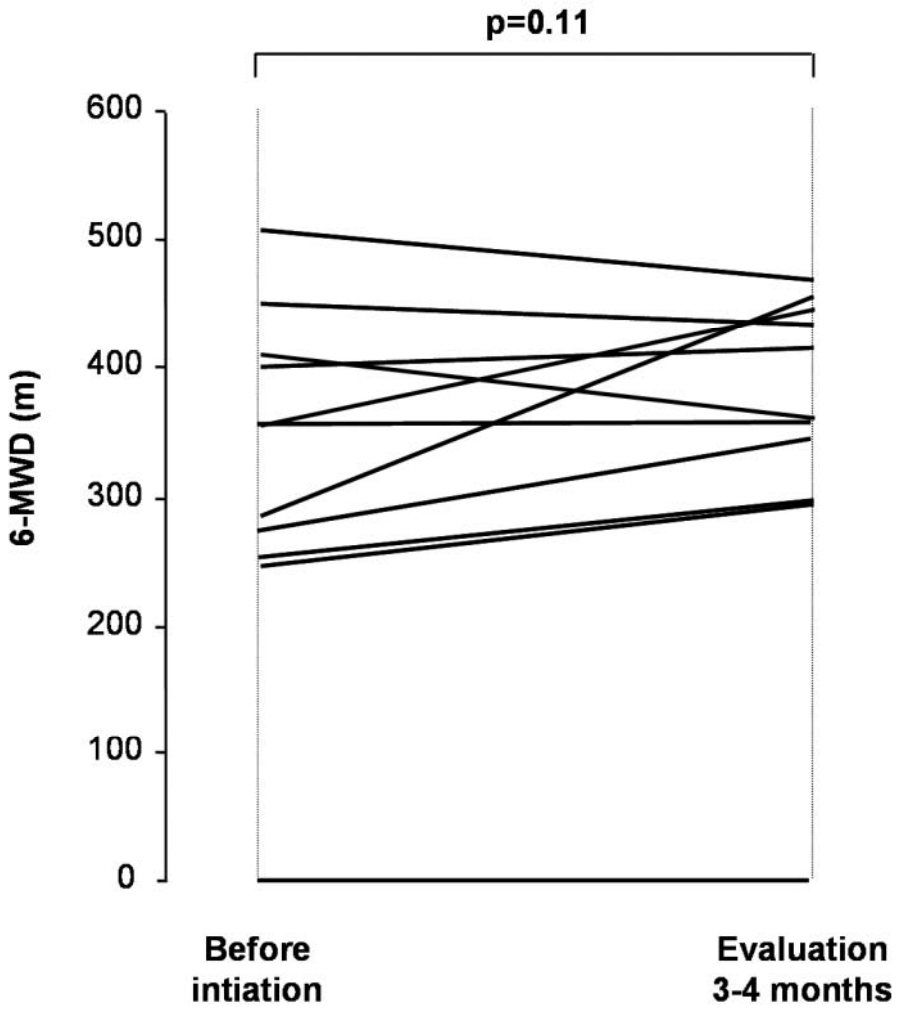
Figure 1. Evolution of NYHA functional class in PVOD patients treated with epoprostenol therapy (n=12).

Eight patients had evaluation at 3-4 months and in 4 patients, NYHA functional class at the last evaluation was reported. Except one patient who died before transplantation, all patients were in NYHA functional class III (7 patients improved from class IV to III, $p<0.01$), but none of them improved to functional class I or II.



<u>Figure 2</u>. Evolution of 6-MWD in PVOD patients treated with epoprostenol therapy.

6-MWD was slightly improved but the difference does not reach statistical significance (+41m, p=0.11).



<u>Figure 3</u>. Evolution of hemodynamic parameters in PVOD patients treated with epoprostenol.

After 3-4 months of epoprostenol therapy, an improvement of hemodynamics was observed with a significant decrease of PVRi (**A**), mPAP (**C**) and a significant increase of cardiac index (**B**) and SvO_2 (**D**).

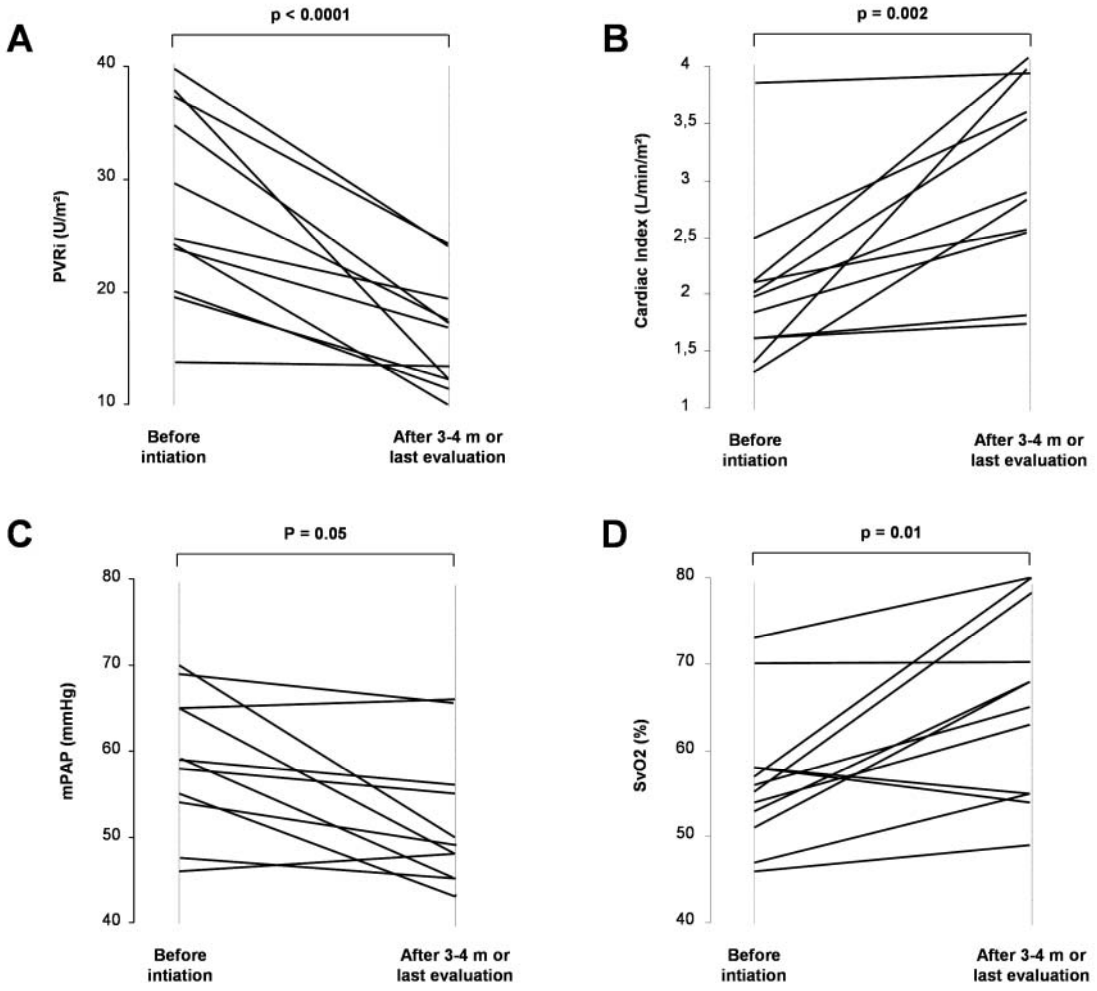


Figure 4.

4A. Time from diagnosis to death or lung transplantation.

The vast majority of PVOD patients were transplanted or died within 24 months following diagnosis of PVOD.

4B. Survival of PVOD patients benefiting from a management strategy combining PAH basic therapy, continuous intravenous epoprostenol and listing for lung transplantation.