Idiopathic Pulmonary Arterial Hypertension: Could We Obtain A Hemodynamic Near Normalization? Clues from Three Long-Term Survivors on Epoprostenol Treatment

Abstract
Pulmonary arterial hypertension is a disease with a poor prognosis characterized by right ventricular failure, due to an increase in pulmonary vascular resistance and pulmonary arterial pressure. The introduction of specific treatments in the past decade has dramatically changed the management of the disease, and the addition of parenteral prostanoids to oral therapy has shown to improve survival in responding patients, as demonstrated by the clinical cases exposed in this paper: three female patients with moderate or severe pulmonary arterial hypertension and advanced NYHA functional class at diagnosis were able to overcome a 10-year survival along with a significant improvement in clinical and hemodynamic status thanks to the introduction of intravenous epoprostenol treatment.

Keywords: Pulmonary arterial hypertension; Epoprostenol; Survival

Case Reports

Patient 1 is a 65-year-old woman with idiopathic pulmonary arterial hypertension (iPAH) diagnosed in 1997 after a rapidly progressive reduction of exercise capacity in the last year. At first evaluation at our center, the patient was in NYHA/WHO functional class III, with a reduced effort capacity (six-minute walk distance - 6MWD 370 meters). ECG showed right ventricular (RV) strain, echocardiography showed marked RV dilatation, with a still preserved systolic function (tricuspid anular plane systolic excursion - TAPSE 22 mm). Right heart catheterization (RHC) revealed a moderate precapillary pulmonary hypertension (mean PAP 42 mmHg, wedge pressure - WP 9 mm Hg, cardiac index - CI 2.6 l/min/m², pulmonary vascular resistance - PVR 7.8 WU – Wood Units), with no acute vasoreactivity to inhaled nitric oxide (iNO, 20 ppm) (Figure 1). At that time, continuous iv infusion of epoprostenol was the only treatment available, so it was started and up-titrated to the maximum tolerated dosage. During the following months we observed a progressive improvement in clinical status and effort tolerance. After 2 years (epoprostenol dose 32 ng/kg/min) she was in class II with a good effort tolerance (6MWD 490 m), and a second invasive evaluation documented an improvement of hemodynamics (mPAP 26 mmHg, CI 2.9 l/min/m², PVR 4.7 WU). In the following 15 years, she improved gradually and currently she is on epoprostenol 59 ng/Kg/min in NYHA/WHO class I with a good effort tolerance (6MWD above 500 meters). ECG and echocardiography show right ventricular reverse remodelling, with normalization of
RV dimensions and regression of RV strain signs. These results are consistent with the last RHC that shows a mild increase of PVR with normal pulmonary pressure (mPAP 22mmHg, CI 2.8l/min/m², PVR 3.6WU) (Figure 1). During this period, the patient experienced only mild side effects due to prostanoids (flushing and tolerable jaw pain). We had to reposition the central venous catheter (CVC) twice due to local infection (6 and 10 years after the first implantation).

**Patient 2** is a 47-year-old woman who received a diagnosis of iPAH in 1999 after progressive dyspnoea and reduction of the exercise capacity in the last 2 years and syncope in the last months. At first evaluation at our centre, the patient was in NYHA/WHO functional class III and had jugular distension, hepatomegaly and peripheral oedema. The 6MWD revealed a marked reduction of effort capacity (270 m), ECG showed RV strain Figure 2a, echocardiography showed marked right heart dilatation with severe RV free wall hypokinesis (TAPSE 12 mm) (Table 1). The RHC revealed a severe pulmonary hypertension (mPAP 57 mmHg, WP 3 mmHg, CI 2.2 l/min/m², PVR 16.4 WU), with no response to the acute vasoreactivity test (iNO, 20 ppm) (Figure 2). Thus, she was started on bosentan 62.5 mg bid, increased to 125 mg bid after 4 weeks. In the first 10 months the patient had an improvement in NYHA/WHO functional class (from III to II), in effort tolerance (from 270 m at baseline to 360 m after 3 months of treatment) and a regression of systemic congestion. At that time RHC confirmed a hemodynamic improvement. During the following year, she had a new reduction of exercise capacity and returned to III NYHA/WHO functional class. A RHC, performed after 2 years of treatment, showed a deterioration of pulmonary hemodynamics (mPAP 50 mmHg, CI 2.4 l/min/m², PVR 12.8 WU) (Figure 3).

**Figure 1:** PATIENT 1: Right heart catheterizations, 6MWD and treatment during follow-up.

**Figure 2:** PATIENT 2: ECG modifications during follow-up.
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On the basis of these results we started iv infusion of epoprostenol. The patient met a rapid improvement of NYHA/WHO functional class (from III to II after 2 months of treatment) and effort tolerance (6MWD from 240 m before epoprostenol to 380 m after 2 weeks, 445 m after 4 months, 485 after 1 year and above 500 m after 4 years of treatment, (Figure 3)). Four years later (epoprostenol 37 ng/Kg/min), RHC showed a considerable improvement of hemodynamic assessment (mPAP 37 mmHg, CI 3.5 l/min/m$^2$, PVR 6.5 WU), reversing PH to a mild stage. Thirteen years after starting epoprostenol, patient is still NYHA/WHO functional class II, 6MWD is stable on 500 m; echocardiography (Table 1) and ECG Figure 2a-b show an improvement of RV eccentricity index and RV strain, respectively. The last catheterization shows a near normalization of pulmonary pressure and a mild elevation of PVR (mPAP 27 mmHg, CI 3.5 l/min/m$^2$, PVR 4.4 WU) (Figure 3). Patient's side effects during follow-up were essentially limited to flushing, jaw pain and episodic diarrhoea.

Patient 3 is a 48-year-old woman who received a diagnosis of iPAH in 1999. Since 1998 she had dyspnoea and progressive reduction of effort tolerance, and these symptoms worsened during the last 2 months of pregnancy. Just few days after the delivery she had an echocardiographic evaluation that showed an estimated systolic PAP of 100 mmHg, so she was referred to our center. At first evaluation, the patient presented jugular distension (1-2/4), hepatomegaly and mild peripheral oedema; she was NYHA/WHO functional class III and showed a decreased exercise capacity (6MWD 330 m, (Figure 4)); ECG showed right ventricular strain; respiratory function tests, perfusion lung scan and autoantiborpal assessment were normal. The patient underwent RHC that confirmed the diagnosis of moderate-severe precapillary PH with positive response to acute vasoreactivity test with iNO 20 ppm (mPAP from 46 to 36 mmHg, CI from 2.8 to 3.6 l/min /m$^2$, PVR from 7.8 to 4.7 WU) (Figure 4). According to these results, the patient was started on a calcium channel blocker (nifedipine 90 mg/die; it was not possible to increase the dose because of severe peripheral oedema). After 1 year of treatment, the patient showed a substantial increase in effort tolerance (6MWT from 330 to 470 m, (Figure 4)), and improvement of NYHA/WHO functional class (from III to II), but in the following 3 months exercise capacity worsened, so oral beraprost was added at the dosage of 40 mg/die and increased at the maximum tolerated dose (400 μg/die). During the first year, the patient had a transient improvement in clinical status and exercise capacity, but during the following months she had a new severe deterioration, returning to NYHA functional class III. We performed a hemodynamic evaluation that revealed a significant worsening of pulmonary hypertension (mPAP 90 mmHg, CI 2.8 l/min/m$^2$, PVR 14.4 WU). Moreover, there was no more vasoreactivity. At that time we discussed the opportunity to start epoprostenol, but the patient refused the implantation of the intravenous line. For this reason we decided to suspend beraprost and nifedipine, and start bosentan (62.5 mg bid for the first 4 week, followed by 125 mg bid). After four months she had minimal clinical improvement and a RHC showed a decrease in PAPm, and PVR but also CI was reduced (mPAP 65 mmHg, CI 2.2 l/min/m$^2$, PVR 13 WU) (Figure 4). So epoprostenol was started and up-titrated to the maximum dosage.
tolerated dosage (up to 46 ng/kg/min during a 10 years follow-up). During this period we obtained a progressive and sustained improvement of clinical status (WHO class II) and effort tolerance (6MWD above 500 m). At the ECG we observed a reduction in RV strain and echocardiography documented a reverse remodelling of RV geometry (Figure 5). RHCs performed 2 and 4 years after starting epoprostenol revealed a progressive improvement of pulmonary hemodynamics (mPAP from 65 mmHg after bosentan treatment to 51 and 36 mmHg, respectively); last evaluation confirmed the results obtained (Figure 4). Flushing and jaw pain were the most frequent side effects referred by the patient during follow-up. Liver function tests have been monthly performed, remaining between normal values. The patient never presented CVC infection in her clinical history.

Discussion

PAH is a progressive disease, with a very poor prognosis if left untreated [7]. In the last decade we witnessed the introduction of specific therapies which showed to improve exercise capacity, NYHA functional class, hemodynamics and progression of disease in several clinical trials [2-6,8-11] Despite the number of PAH patients on treatment is increasing worldwide, there are no data published on patients with a very long survival and a good hemodynamic response. In this paper we report three iPAH cases
with a very long survival (>10 years), impressive hemodynamic response (almost normalization of PVR) ad reverse remodelling of the RV. This response to specific treatment is uncommon and is similar to the results obtained in the minority of patients who could be treated with calcium channel blockers (CCB) [12]. Among our cases, only one patient was vasoreactive, but she had limited benefit by CCB; after few months she had a severe deterioration as she lost pulmonary vasoreactivity. Thus our patients had “fixed” PVR when epoprostenol was started, and the very significant reduction in PVR after long-term treatment raises the question if it is possible to achieve the regression of the pulmonary arteriopathy responsible of the clinical syndrome. Several studies demonstrated that prostanoids have antiproliferative effects in vitro [13-16] and can prevent or reverse the pulmonary arteriopathy in animal models of pH [17]. A similar mechanism could be present in human, as suggested by the fact that patients, who did not have acute hemodynamic benefit during acute vasodilator challenge, had clinical and hemodynamic benefit during chronic epoprostenol treatment [18]. The results of our patients are even more impressive with the near normalization of PVR, RV anatomy and function. In our opinion, the magnitude of this improvement suggests that in a small subgroup of non-vasoreactive patients with iPAH it might be possible to obtain a reverse remodelling of the obstructive arteriopathy. This hypothesis should be confirmed by the analysis of large registries which are currently ongoing [19-21], and it should foster collaborative studies among referral centers looking at these patients with a particular good response to therapy.

References