CASE REPORTS

Long-term echocardiographic follow-up of a patient with primary pulmonary hypertension receiving iloprost inhalations

Eirik Pettersen, Torstein Holm Morstøl, Johnny Aage Vegsundvåg

Department of Cardiology, Rikshospitalet, 0027 Oslo
Department of Internal Medicine, Ålesund Hospital, 6026 Ålesund

Received 27 January 2004; received in revised form 4 May 2004; accepted 15 June 2004
Available online 13 August 2004

Abstract Iloprost inhalation has recently emerged as an alternative therapy for severe primary pulmonary hypertension. In the studies documenting the effect of iloprost inhalation therapy, hemodynamic variables have been measured invasively. We have followed a patient with primary pulmonary hypertension receiving iloprost inhalation therapy for 5 years using echocardiography to monitor changes in pulmonary artery pressure and right ventricular function. Echocardiography was also used to evaluate the initial response to iloprost inhalation therapy. This case illustrates the feasibility and utility of echocardiography in the testing and follow-up of iloprost inhalation therapy in patients with pulmonary hypertension.

Keywords Primary pulmonary hypertension; Echocardiography; Iloprost

Introduction

Primary pulmonary hypertension (PPH) is a rare condition (estimated incidence of one to two cases per million in the general population) that causes disabling symptoms and if untreated leads to an early death. Several studies have shown that continuous epoprostenol (prostacyclin) infusion improves exercise tolerance, hemodynamics and survival in patients with PPH. Inhalation of the stable prostacyclin-analogue iloprost has emerged as an alternative therapy for severe PPH, as documented in several studies. Inhalation therapy eliminates the systemic side effects of continuous intravenous infusion and the risk of infection associated with an in-dwelling catheter. Right ventricular function is an important factor in the outcome of patients with PPH, and we applied easy-to-use echocardiographic measures of right
ventricular systolic and diastolic function, stroke volume, tricuspid regurgitation and pulmonary arterial pressure to evaluate the initial response to iloprost inhalation therapy and to monitor changes in pulmonary artery pressure and right ventricular function during a follow-up period of 5 years. The present case report illustrates both the successful use of this new treatment with iloprost inhalation and the feasibility and utility of echocardiography in the testing and follow-up of this therapy in patients with pulmonary hypertension. The patient’s informed consent for the publication of this report has been obtained.

Case report

A 33-year-old woman was admitted to hospital in November 1998 after syncope on slow walking. She had over the two previous years experienced increasing exertional dyspnoea, vertigo and fatigue, and several syncopes on exertion. In the months prior to her admittance, she had also suffered from upper abdominal pain and nausea. The patient had three children aged 3, 5 and 7 years, all the pregnancies were uneventful. There was no history of hereditary diseases in her family or case of sudden death.

On admittance, her blood pressure was 130/79 mmHg, pulse rate 102/min, and there was no peripheral oedema. Auscultatory findings over the lungs were normal. On auscultation of the heart, a systolic murmur grade 3/6 was heard at the lower left sternal border. Laboratory tests were all normal (including serology and tests for collagen vascular diseases and thrombophilia), except for a slightly elevated creatinine at 114 μmol/L. Arterial blood gas levels were normal. Chest X-ray revealed an enlarged heart. Lung perfusion and ventilation scintigraphy, spirometry and lung CT-scan were all normal. Continuous measurement of arterial oxygen saturation showed an average of 97% during the daytime, but during sleep the patient’s saturation repeatedly fell below 90%, and half of the time it was between 75 and 84%.

Echocardiography showed moderate right ventricular hypertrophy and dilatation with an end-diastolic diameter of 6.5 cm in the short axis view and systolic flattening of the interventricular septum. There was reduced systolic function of RV with a tricuspid annular plane systolic excursion (TAPSE) of 1.1 cm, where TAPSE was defined as the difference in the displacement of the right ventricular base during diastole and systole. There was also a large tricuspid regurgitation (TR) with a maximal pressure gradient of 82 mmHg and a small pulmonary regurgitation with an end-diastolic pressure gradient of 25 mmHg. The inferior vena cava (IVC) was dilated and showed only 10% variation in calibre during quiet regular respiration. The left ventricle was semi-compressed with delayed diastolic filling as shown by transmitral flow measurement. Systolic function was normal. There was no pericardial effusion and no significant aortic or mitral valvular pathology. No shunts or congenital defects were found.

Angiography of the pulmonary arteries showed dilated central vessels with abnormally thin peripheries. Measurements of pulmonary artery pressure were compatible with PPH (November 1998 in Table 1).

Treatment was initiated with diuretics, warfarin, supplemental oxygen during sleep and nifedipine, on which the patient improved slightly both clinically and hemodynamically. After an increase in nifedipine dosage, the patient’s clinical condition deteriorated from New York Heart Association functional class (NYHA) 3 to NYHA 4 together with worsening of hemodynamic values (Table 1). Nifedipine was reduced, digitoxin treatment was started, and the patient clinically improved to NYHA 3.

A recent report had shown marked improvement in a patient with PPH treated with inhalation of aerosolised iloprost, and a trial of iloprost inhalation was performed. Ten micrograms of iloprost (Ilomedin, Schering AG, Berlin, Germany) was diluted in isotone saline solution (5 μg/mL), and nebulized (Freeway Lite II with side stream nebulizer, Profile Respiratory Systems, Bognor Regis, West Sussex, England), and inhaled over a period of 10 min. The procedure was repeated after 35 min. The test showed a significant acute response with an increase of systemic stroke volume (expressed as the velocity–time integral in the left ventricular outlet tract (LVOT-VTI)) of 34% together with an increase of right ventricular systolic function measured by TAPSE (Fig. 1). This favourable hemodynamic response was interpreted as a probable iloprost-induced vasodilatation with reduction of the pulmonary arterial resistance. The patient was thereafter given inhalations of a nebulized dose of 20 μg iloprost every 2 h (not during sleep). On this regimen, her clinical condition gradually improved, as did hemodynamic values measured by echocardiography.

After 2 months of treatment her functional class had improved to NYHA 2A. Since June 1999 the inhalation regimen has been simplified to a nebulized dose of 20 μg iloprost five times daily. Approximately 6 months after initiation of iloprost therapy, the patient was without symptoms.
(NYHA 1), supported by hemodynamic values measured by both echocardiography and catheterisation (Table 1). The patient has since been stable in this condition and has not experienced any side effects of the iloprost therapy over a period of 5 years. Consequently, we have not found any reason to change the inhalation dose or frequency.

Discussion

Echocardiography is a well-established diagnostic procedure for pulmonary hypertension. In addition to obtaining an estimate of systolic pulmonary artery pressure, right ventricular function, important classification of severity and prognosis, can be evaluated. We chose easy-to-use measures to get a comprehensive and integrated information of the right ventricle’s systolic function, filling pressure, degree of tricuspid regurgitation and stroke volume. TAPSE has been shown to correlate well with right ventricular ejection fraction, and the same study shows values in the reference group consistently above 15 mm. Since diastolic tricuspid Doppler signals are of limited value in the setting of significant tricuspid regurgitation, we applied variation (%) in IVC diameter during quiet regular respiration. This parameter provides an estimate of right atrial pressure, and Kircher et al. 

Table 1

<table>
<thead>
<tr>
<th>Medication</th>
<th>NYHA class</th>
<th>TAPSE (cm)</th>
<th>TR grade (0–3)</th>
<th>TR variation (%)</th>
<th>LVOT-VTI (cm)</th>
<th>SPAP (mmHg)</th>
<th>DPAP (mmHg)</th>
<th>MPAP (mmHg)</th>
<th>MRAP (mmHg)</th>
<th>PAR (dyn.s.cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O 40 N₂O 240</td>
<td>3A</td>
<td>3.1</td>
<td>1.5</td>
<td>1.5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>N₂O 300</td>
<td>2B</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 240</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 160</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 60</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>N₂O 120</td>
<td>2A</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association, N₂O = nitrous oxide, TAPSE = tricuspid annular plane systolic excursion, TR = tricuspid regurgitation, LVOT = left ventricular outflow tract, VTI = velocity-time integral, SPAP = systolic pulmonary arterial pressure, DPAP = diastolic pulmonary arterial pressure, MPAP = mean pulmonary arterial pressure, PAR = pulmonary arterial resistance.

Although we did not measure pulmonary vascular resistance (PVR) invasively during the first inhalation trial, with an augmentation in cardiac output of 34% together with an almost unchanged TR pressure gradient and stable heart rate, one can assume a fall in PVR of at least 20%. This may illustrate the point made by other authors that initial responders to iloprost inhalation therapy (defined as a fall in PVR of at least 20% during first trial) have a better long-term prognosis than non-responders. Following onset of iloprost inhalation therapy, the TR pressure gradient did not immediately decrease, either in the acute phase (during...
and immediately after inhalation) or during the first month. This is most likely due to the fact that the pulmonary vasodilatation results in a decrease in right ventricular afterload allowing an increase in right ventricular output, and the result is an unchanged or even increased TR pressure gradient. Our data suggest that, during testing and the initial phase of therapy, cardiac output is a better measure of response to treatment.

After 2 months of therapy, however, the TR pressure gradient fell. This probably reflects an antiproliferative effect of iloprost on the pulmonary vascular bed. Iloprost is a potent pulmonary vasodilator, but it also has additional effects relevant to its therapeutic use in patients with PPH. In addition to decreasing vascular tone, iloprost inhibits media hypertrophy, fibroblast chemotaxis and growth, and platelet and granulocyte interaction, all of which contribute to the vascular remodelling process in primary pulmonary hypertension.

The degree of right ventricular dysfunction measured by echocardiography showed a good correlation to the clinical picture, exercise testing and hemodynamic variables measured by catheterisation (Table 1). Echocardiography was found to be very suitable for monitoring the improvement of the patient, with gradual reduction of the pulmonary artery pressure, reduction of TR, and normalisation of TAPSE, right ventricular filling pressure and stroke volume. In addition, ventricular shapes and dimensions gradually normalised, with normalised left ventricular diastolic function as measured by transmitral flow. The right ventricle has, since normalisation of its filling pressure and reduction of TR, shown delayed diastolic filling by transtricuspid measurements.

The patient repeatedly showed hypoventilation during sleep, without clinical signs of airway obstruction. This is a relatively common finding in patients with PPH. We speculate that this probable central hypopnea with low arterial oxygen saturation during night was caused by low cardiac output secondary to PPH with right ventricular failure, and this hypoxemia may have worsened the development of PPH in this patient. Supplemental oxygen therapy during sleep was sufficient to normalise the arterial oxygen saturation, which may have contributed to the patient’s subsequent improvement.

Our patient remains stable in her asymptomatic state 5 years after onset of treatment with inhalations of aerosolised iloprost. To our knowledge, there have been no published reports with a follow-up period this long on this treatment. Considering that PPH is a progressive disease, her now stable condition must be viewed as a therapeutic success.

**Conclusion**

This case emphasizes the value of echocardiography in the selection of appropriate therapy and long-term follow-up of a patient with primary pulmonary hypertension. The degree of right ventricular dysfunction measured by echocardiography showed a good correlation to the clinical picture and hemodynamic variables measured invasively. This case report demonstrates the
feasibility of monitoring the hemodynamic effects of iloprost inhalation therapy non-invasively, thus avoiding the need for frequent right-sided catheterisation.

References


