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# *Case Report*

# Sildenafil in the Management of Childhood Severe Idiopathic Pulmonary Arterial Hypertension: A Case Report

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**Abstract** Prognosis is poor in children with severe idiopathic pulmonary arterial hypertension who present with progressive downhill course. We report the use of oral sildenafil in a 13-year-old girl with suprasystemic idiopathic pulmonary arterial pulmonary hypertension. This therapy improves her quality of life and optimizes the chance of successful lung transplantation.

**Key words** Paediatrics; Pulmonary arterial hypertension; Sildenafil

## Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a serious and progressive condition. Without treatment, the prognosis is poor particularly in children, with a medium survival of only 10 months from the time of diagnosis.[1] Calcium channel antagonist is only efficacious in about 40% of paediatric patients with IPAH.[2] Difficulty in drug administration, high cost and undesirable side effects of continuous intravenous prostacyclin limited its use in children. In this article, we report an adolescent girl with severe IPAH that was refractory to conventional vasodilator and the successful treatment using oral sildenafil. This therapy significantly improves her quality of life and optimizes the chance of successful transplantation. The rational of choosing sildenafil among other medications is discussed.

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## Case Report

In 1992, a 2.5-year-old Chinese girl presented with one-month history of dyspnoea and cyanosis on exertion. She enjoyed good health prior to the onset of symptoms. There was no relevant family or drug history. On physical examination, she was mildly cyanosed with clubbing of fingers. Her precordium was hyperdynamic and the apex was laterally displaced. The second heart sound was widely splitted with an accentuated pulmonary component. A grade 3/6 pansystolic murmur was noted at the left lower sternal border.

Electrocardiogram showed right axis deviation and right ventricular hypertrophy while chest X-ray revealed cardiomegaly and prominent pulmonary trunk. Initial transthoracic echocardiogram demonstrated dilatation of right atrium, right ventricle and main pulmonary artery. No other structural heart lesion was evident. There was severe tricuspid regurgitation with a Doppler estimated velocity of 5.2 m/s, which suggested systemic level of pulmonary artery pressure. Cardiac catheterisation confirmed systemic pulmonary artery pressure with elevated pulmonary vascular resistance of 17.9 Wood unit · $m^2$ and low cardiac index of

2.9 L/min/$m^2$ (Table 1). Administration of intravenous nifedipine produced no change in haemodynamics.

Secondary causes of pulmonary arterial hypertension including HIV infection, portal hypertension, connective tissue diseases were excluded by various laboratory tests. Chronic thromboembolic disorders were excluded by negative thrombophilia screen and normal magnetic resonance pulmonary angiography. Pulmonary function test did not suggest primary lung disease. Ventilation perfusion lung scintiscan revealed non-segmental patchy perfusion defects over both lungs compatible with idiopathic pulmonary arterial hypertension.

Oral nifedipine, being the only effective oral vasodilator for pulmonary hypertension in the early 1990s, was commenced. However, her general condition gradually deteriorated over the years. At the age of 11, she was admitted to paediatric intensive care unit with an episode of severe haemoptysis. Since then, her condition went on a progressive downhill course. Besides having recurrent episodes of mild haemoptysis, her severely limited exercise capacity was equivalent to New York Heart Association Functional Class III. Restudy cardiac catheterisation in 2001 demonstrated suprasystemic pulmonary artery pressure with pulmonary vascular resistance of 46.1 Wood unit · $m^2$ (Table 1) and showed no reversibility following administration of 40 ppm nitric oxide with 100% oxygen. Transesophageal echocardiogram demonstrated a small (11 mm) secundum atrial septal defect with right to left shunt. We believed that her diagnosis was IPAH because Eisenmenger syndrome associated with a small atrial septal defect presenting at 2.5 years of age was extremely unlikely. Instead the presence of the atrial septal defect probably prolonged her survival.

Since 2001, she has been on the waiting list for lung transplantation. Nifedipine was discontinued in the absence of response and ambulatory oxygen therapy was prescribed. Systemic anticoagulation was contraindicated with the history of haemoptysis. Continuous intravenous prostacyclin was considered not a good choice due to the enormous cost (estimated cost of HK$30,000-305,000 per month for dosage of 4-40 ng/kg/min) and the potential complications associated with the complex drug administration method. Oral sidenafil (Viagra; Pfizer) was commenced in April 2004. The initial dose was 25 mg tid and was subsequently stepped up to 50 mg tid with no side effects recorded.

At one month follow-up, her exercise capacity in terms of 6 minute walk test (6MWT) improved significantly compared with baseline measurement (300 m vs 210 m).

**Table 1** Results of cardiac catheterisation in 1992 and 2001

| | 1992 | 2001 |
|---|---|---|
| RAP (mmHg) | 6 | 10 |
| PAP (mean) (mmHg) | 90/35 (60) | 145/83 (110) |
| BP (mean) (mmHg) | 95/65 (80) | 109/69 (86) |
| PWP (mmHg) | 6 | 10 |
| PVR (Wood unit · $m^2$) | 17.9 | 46.1 |
| Cardiac index (L/min/$m^2$) | 2.9 | 3.1 |

RAP: mean right atrial pressure; PAP: pulmonary arterial pressure; BP: simultaneous systemic blood pressure at descending aorta; PWP: mean pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance calculated by Fick Principle

The improvement in 6MWT was sustained at 6 months (306 m) and 12 months (290 m) afterwards. Her oxygen saturation was maintained at around 80% in room air. Serial right ventricular systolic pressure estimated by Doppler at 2 and 3 months, demonstrated significant reduction whilst the right ventricular performance index (Tei Index) improved, though the effect was less impressive at 12 months (Figure 1). Her quality of life continued to improve without obvious side effects.

## Discussion

IPAH is defined as a sustained elevation of pulmonary arterial pressure (≥25 mmHg at rest or ≥30 mmHg during exercise) without a demonstrable cause. It is a rare disorder with female predominance (F:M = 1.7-3.5:1). The non-specific symptoms often result in delayed diagnosis. Prognosis is poor in children who do not respond to conventional therapy and early death is almost inevitable in some cases. From our experience, all our paediatric patients with IPAH except this girl died within 2 years after diagnosis (unpublished hospital data).

Despite significant advances in the study of pathobiology of IPAH, the mechanisms of this disease remain speculative. Endothelial dysfunction is now recognised to play a crucial role in its pathogenesis. The impaired production of vasodilators such as nitric oxide and prostacyclin, along with over-expression of vasoconstrictors such as endothelin-1, thromboxane A2, not only increase vascular tone but also promote a procoagulant state and vascular remodeling leading to progressive vascular obstruction and obliteration. Novel therapies targeting at these mediators have brought hopes to this incapacitating condition.

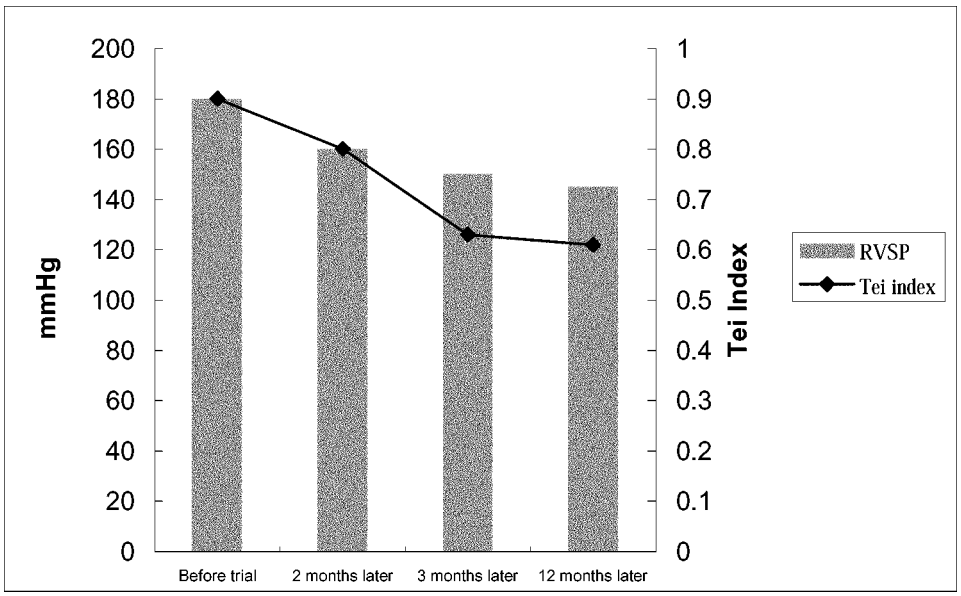


**Figure 1** Haemodynamic data from serial echocardiograms. RVSP: estimated right ventricular systolic pressure by Doppler interrogation of tricuspid regurgitation. Tei index: Doppler derived global myocardial performance index of right ventricle (Normal 0.32±0.03).

## Conventional Therapies

Conventional therapies for IPAH include systemic anticoagulation with warfarin, diuretics, oxygen therapy and calcium channel antagonist. Warfarin improves survival and quality of life in patients with IPAH[2] whereas calcium channel antagonists are beneficial in about 20% of adults and 40% of paediatric patients rising the 5 year survival rate to more than 90%.[2] On the other hand, the systemic vasodilatory and negative inotropic effects of calcium channel antagonists may be detrimental in non-responders especially those with severe right heart failure.

## Continuous Intravenous Infusion of Prostacyclin (Epoprostenol)

Prostacyclin is a potent endogenous vasodilator with antiplatelet, antiproliferative and cytoprotective properties. Continuous intravenous infusion of prostacyclin significantly improves haemodynamics, functional status and prolongs survival in patients with severe IPAH irrespective of vasoreactivity.[3] It is associated with a 5 year survival rate comparable with or even better than that after lung transplantation. Nevertheless, frequent minor adverse reactions, potentially life-threatening complications related to the complex delivery system, high cost and drug tolerance make prostacyclin far from ideal as the first line therapy for IPAH especially in children.

## Other Medical Therapies for Pulmonary Hypertension

Because of the problems associated with intravenous prostacyclin, other prostacyclin analogues have been invented. Preliminary study on treprostinil, a subcutaneous prostacyclin analogue demonstrated short-term benefits.[4] However, treprostinil is not available in Hong Kong and the continuous subcutaneous infusion is associated with unpleasant local reaction. Beraprost, an orally active prostacyclin analogue was shown to have beneficial effects that could not be maintained after nine months.[5] Beraprost is also not available locally. Iloprost, an inhaled prostacyclin analogue appears to be an effective drug.[6] However, the need of frequent regular inhalation (6 to 9 times a day) and the high cost (HK$23,000 per month) make it not an ideal choice for our patient. The orally administered nonselective dual endothelin receptor anatagonist, bosentan is efficacious in both adult and paediatric patients.[7,8] Unfortunately the high cost of this drug (HK$25,000-50,000 per month) hinders its use in our case.

## Sildenafil

Sildenafil, a highly selective potent inhibitor of phosphodiesterase type 5 (PDE5) is an established treatment of erectile dysfunction in men. It potentiates smooth muscle relaxation via a nitric oxide-dependent increase of cyclic guanosine 5-monophosphate in the corpus cavernosum as well as the lungs where PDE5 is abundant. Description of the use of sildenafil in childhood IPAH is limited to few isolated case reports.[9,10] It was not until recently the first multicentred, randomised, double-blind, placebo-controlled crossover study on sildenafil became available.[11] This 12 week-trial confirmed the beneficial effect of sildenafil on exercise tolerance, cardiac index and quality of life in patients with IPAH. The safety of sidenafil has already been established at least for standard dose (50-100 mg) admitted intermittently for erectile dysfunction.

In view of the deteriorating condition of our patient, we decided that a pulmonary selective vasodilator should be given to improve her quality of life and make the wait for lung transplantation possible. Sildenafil was chosen as it was readily available, easy to administer and relatively cheaper than other new pulmonary vasodilators. Treatment with sildenafil 150 mg per day costs about HK$4,000 per month which was 5-10 times cheaper than bosentan and 10-60 times cheaper than intravenous prostacyclin. The dosage was similar to that used in adult studies and was well tolerated. The effect was very encouraging with significant improvement in functional capacity and reduction in pulmonary arterial pressure.

## Conclusion

The choice of medical therapy for individual patient with severe IPAH is complex and requires consideration of multiple factors including the physician's experience, patient's preference, level of evidence on the efficacy of different therapies, drug availability, adverse effect and cost.[12] This case report contributes to a building sense of excitement that sildenafil is effective in treating severe IPAH and is well tolerated in children. The long term efficacy and safety of sildenafil and its additive effect with other drugs await further evaluation.

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