Primary pulmonary hypertension (PPH) is an uncommon disorder of unknown etiology characterized by a progressive elevation of pulmonary artery pressure with secondary right ventricular heart failure (1, 2). Survival seldom exceeds five years. A number of vasodilating agents, including oral anticoagulants, nitroprusside, calcium channel blockers, inhaled nitric oxide (NO), and analogues of prostacyclin, including beraprost, iloprost and epoprostenol, have been tested during cardiac catheterization for their acute hemodynamic effects and to form the basis for long-term therapy consideration. Due to the lack of selectivity for the pulmonary vasculature, only a few patients respond to calcium antagonists or nitroprusside (3). Inhalation of NO has been shown to improve gas exchange and right ventricular performance in various settings of pulmonary hypertension (PH) (4). However, long-term treatment of PH with inhaled NO is practically impossible due to the extremely short half-life of NO. Continuous infusion of the prostacyclin analog IV epoprostenol has been shown to reduce mortality rates from PPH. However, catheter infection and tachyphylaxis may limit its applicability, and the cost of treatment is very high (5).

Sildenafil is widely used to dilate penile arteries in patients with erectile dysfunction (ED) (6). The agent is a selective and potent inhibitor of cyclic guanosine monophosphate (cGMP) phosphodiesterase type 5 (PDE-5), which catalyses hydrolysis of cGMP. Inhibition of PDE-5 increases the cellular levels of cGMP by blocking its degradation to 5'-GMP, and leads to vascular smooth muscle relaxation (7). Because PDE-5 is abundant in the lung as well as penile tissues, it has been hypothesized that the drug can also be used to dilate pulmonary arteries in patients with PH as well as the patients with ED (8).

In animal models, sildenafil induced pulmonary vasodilation by a NO-dependent mechanism without decreasing systemic artery pressure (9). Since the first report that sildenafil attenuates acute pulmonary hypertension (PH) associated with withdrawal of inhaled NO in infants with PH complicating congenital heart diseases (10), evidence has accumulated that oral sildenafil may be beneficial as a selective pulmonary vasodilator in patients with not only primary but also secondary PH (11–13).

In this issue, Kataoka and colleagues report a case suggesting that oral sildenafil can be safely considered as an alternative option to IV epoprostenol therapy in patients with severe PPH (14).

Continuous IV epoprostenol has altered the natural history of PH and becomes currently the medical standard of care for patients with PH. However, it is also true that life-threatening complications while receiving IV epoprostenol have been experienced by a number of patients with PPH. Furthermore, increasing doses of epoprostenol are often required to maintain its efficacy. This is, at least in part, due to prostacyclin-induced desensitization. Prostacyclin acts by binding to a G protein-coupled receptor (GPCR) which directly stimulates the enzyme adenylate cyclase (AC) that converts ATP to the second messenger cAMP (15). However, chronic treatment with prostacyclin analogues induces desensitization by inhibiting AC activity and stimulating the activity of phosphodiesterase type 3 (PDE-3), the enzyme that degrades cAMP to 5’AMP in a PKA dependent manner (16). Indeed, the patient reported by Kataoka et al (14) initially responded to IV epoprostenol, which was suggested by the reduction of BNP levels, and then became resistant to the agent until oral sildenafil was co-prescribed. The combination of sildenafil and prostacyclin makes sense from the perspective that an increase in cGMP by sildenafil inhibits PDE-3 and in turn leads to increasing levels of cAMP (16, 17). Sildenafil may form a compensatory mechanism in the pulmonary vasculature falling to desensitization to prostacyclin (Fig. 1). The fact that sildenafil selectively dilates pulmonary vascular beds by a cGMP-dependent mechanism has conferred a promising therapeutic possibility for patients with PH. However, the possibility that sildenafil could exert more pronounced hemodynamic effects when combined with prostacyclin should be emphasized. This hypothesis is supported by the observation by Wilkens et al that the addition of iloprost inhalation provides further improvement in PPH patients after sildenafil has caused long-lasting reductions in mean PAP and pulmonary vascular resistance (18).

Positive responses to vasodilating agents in PH are associated with improved long-term clinical outcomes. A number of studies have reported that sildenafil improves exercise tol-
erance and the quality of life as well as hemodynamic parameters in patients with primary and secondary PH. Further studies are necessary to address issues of long-term safety and the efficacy of sildenafil as well as its synergistic effects with other treatment entities such as prostacyclin analogues, inhaled NO, L-arginine and the endothelin receptor blocker, bosentan.

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References

17) Maurice DH, Haslam RJ. Molecular basis of the synergistic inhibition of platelet function by nitrovasodilators and activators of adenylate cyclase: inhibition of cyclic AMP breakdown by cyclic GMP. Mol

Figure 1. Synergistic interaction between PDE-5 inhibitor and prostacyclin for vascular relaxation. GC: guanylate cyclase, AC: adenylate cyclase, GPCR: G protein-coupled receptor, PKG: cGMP-dependent protein kinase, PKA: cAMP-dependent protein kinase.