Dose-Dependent Reduction in Pulmonary Vascular Resistance With Epoprostenol in Pulmonary Arterial Hypertension

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Prostacyclin (PGI₂), discovered by Moncada et al in 1976,¹ is one of the most potent intrinsic vasodilators with antiproliferative effects and is produced by endothelial cells. Endothelial cells also secrete one of the most potent intrinsic vasoconstrictors with smooth muscle mitogen effects, endothelin (ET), discovered by Yanagisawa et al in 1988.² Both of these discoveries strongly promoted further developments in the field of vascular biology, in which the endothelium might have an important role to play in governing peripheral blood flow.

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These biological developments resulted in clinical application after the 1980s. A typical example is epoprostenol (EPO; Flolan, Glaxo Smith Kline, Brentford, UK), which became commercially available in the United States in 1995 and in Japan in 1999, and created a new era in the treatment of patients with pulmonary arterial hypertension (PAH).

PAH is characterized by a progressive increase in pulmonary vascular resistance (PVR) that eventually leads to right ventricular failure and death. The median survival of patients entered in the NIH registry has been reported as 2.8 years after diagnosis.³

Endothelial dysfunction is common in PAH, and includes increased production of vasoconstrictor/mitogenic compounds such as ET and thromboxane, and decreased production of vasodilator/antiproliferative substances such as PGI₂.^{4,5} Therefore, EPO therapy was theoretically hypothesized to improve the hemodynamics and vascular remodeling observed in patients with PAH.

After the advent of EPO, numerous reports confirmed that its infusion decreased pulmonary arterial pressure and increased cardiac output, resulting in a decrease in PVR or total PVR (TPR) and improved exercise capacity as well as quality of life (QOL). Moreover, with intravenous EPO, survival rates were improved compared with historical controls with idiopathic PAH.^{6–8} Thus, EPO has been the mainstay of PAH therapy for more than a decade. To use EPO more effectively in the clinical situation, it is necessary to understand the specific action of EPO in the various forms of PAH.

In 1997 Califf et al⁹ noticed a critical adverse result of EPO therapy in patients with left ventricular (LV) failure. They administered EPO (4.0 ng·kg⁻¹·min⁻¹) to 237 patients with

severe LV failure and although the cardiac index increased from 1.81 to 2.61 L·min⁻¹·m⁻², pulmonary capillary wedge pressure decreased from 24.5 to 20.0 mmHg, and systemic vascular resistance decreased from 20.8 to 12.3 Wood units, so the trial was terminated early because of the increased death rate (48% in 6 months) and no improvement in walking distance or QOL. A critical adverse result for patients with this type of secondary pulmonary hypertension (PH) stands in sharp contrast to the benefits of EPO in cases of idiopathic PH. The reason for this contrast is not yet fully understood.

In 1999 Rich and McLaughlin¹⁰ discussed excessive doses of EPO. They described how a high cardiac output state (12 of 55 patients) produced by EPO could be changed from 7.4±1.4 to 4.0±0.7 L·min⁻¹·m⁻² without worsening the patient's clinical state by reducing the EPO dose from 98±61 to 60±50 ng·kg⁻¹·min⁻¹. Based on this report, approximately 40–60 ng·kg⁻¹·min⁻¹ has been considered as the maximum range of the EPO dosage.

In 2002 Sitbon et al¹¹ made a detailed and comprehensive report on the efficacy of EPO. They described 178 patients with PAH in New York Heart Association (NYHA) functional class III or IV with EPO (14±4–21±7 (range 8–40) ng·kg⁻¹·min⁻¹) and, after 1 year, mean pulmonary artery pressure (mPA) decreased from 68±14 to 60±12 mmHg, TPR from 37.3±10.5 to 25.0±6.9 Wood units (TPR ratio 67% after EPO), and the 5-year survival ratio increased to 55%. They also reported that the baseline variables associated with a poor outcome were a history of right heart failure, NYHA functional class IV, 6-min walk distance ≤250 m, right atrial pressure ≥12 mmHg etc. From their report, the limitation of EPO (dose ≤40 ng·kg⁻¹·min⁻¹) was recognized, leading to a proposal of combination therapy, which had the effect of minimizing the number of monotherapy-oriented studies.

In this issue of the Journal, Akagi et al proposed a new therapeutic strategy for implementing high-dose EPO monotherapy.¹² They reported that 14 patients with PAH in NYHA functional class III or IV were treated with high-dose (>40 ng·kg⁻¹·min⁻¹) EPO (107±40 (range 54–190) ng·kg⁻¹·min⁻¹) for 1,355±627 days, and that mPA decreased from 66±16 to 47±12 mmHg, PVR from 21.6±8.3 to 6.9±2.9 Wood units, and more importantly, all the patients survived for a period of 3.7 years.

Hemodynamic improvement in PAH is indicated by PVR (TPR) reduction. **Figure** shows the relationship between

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EPO dose ($\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and the PVR (TPR) ratio (%) after EPO in previously reported studies of EPO monotherapy.^{6-8,11-15} A statistically significant exponent relationship was observed ($R^2=0.92$). In the 2 studies of high-dose EPO therapy, PVR showed almost the same ratio after EPO of approximately 30%.^{10,12} And, more importantly, none of the patients died in either of those studies, despite having severe PAH in which the baseline PVR was 12.8 and 21.6 Wood units, respectively.^{10,12}

It is, of course, important that patients receiving high-dose EPO should be closely monitored for side-effects. Akagi et al used cardiotonic drugs, including 3–5 γ dobutamine when systolic blood pressure could not be kept above 90 mmHg, or when the value of SvO₂ was less than 60%, or when right heart failure was not improved. They also gave intensive supportive treatment to patients to help them tolerate the side-effects during the infusion of high-dose EPO, including jaw pain, leg pain, headache, flushing, eruption, nausea and diarrhea. After all these efforts of the patients and the therapeutic team, the target dosages were achieved.¹²

Many medications other than EPO are now available or will be available in the near future, such as ET receptor antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulator, several growth factor inhibitors etc. Although the new era is welcomed, we do not yet have a thorough understanding of the new drugs' usages and interactions contributing to improved QOL and prolonged lifespan, and it may also still be difficult to achieve longer survival for the present patients with severe PAH.

One of the challenging trials, the high-dose EPO monotherapy report from Japan leads us to conclude that the effect of EPO on PVR reduction may be dose-dependent over a wider range than we expected (Figure), which will strongly encourage future exploration of effective treatment options for managing patients with severe PAH.

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