Long-Term Epoprostenol Therapy in Pulmonary Artery Hypertension

Sequence of Changes in Hemodynamic Effects

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Background: Sequential changes in the hemodynamic effect of chronic epoprostenol therapy raise the following questions. Does an increase in cardiac output (CO) precede lowering of the pulmonary artery pressure (PAP) over the time course of improvement? What are the characteristics of good responders to chronic epoprostenol treatment?

Methods and Results: Hemodynamics were evaluated by catheter examination. Most patients still alive after >1 year showed an increase in CO either with no change in mean PAP or accompanied by a decrease in mean PAP during increased dosing of epoprostenol. Immediately before cessation of the increase in epoprostenol dose in good responders, the ratio of total pulmonary resistance to total systemic resistance was low, and the pulmonary artery wedge pressure minus right atrial pressure was high compared with the newest data in poor responders. One year after fixing at the best dose of epoprostenol, the mean PAP further decreased.

Conclusions: In good responders, pulmonary selectivity to epoprostenol is high, and the blood returning to the left-sided heart through the pulmonary circulation increases. Hemodynamics further improve, even after fixing at the best dose of epoprostenol. The present data did not show that an increase in CO precedes lowering of the PAP over the course of improvement. (Circ J 2009; 73: 523–529)

Key Words: Cardiac index; Pulmonary artery pressure; Pulmonary vascular selectivity; Total pulmonary resistance

Chronic epoprostenol infusion ameliorates the hemodynamics and prognosis of pulmonary artery hypertension (PAH);^{1–5} which progresses early with an elevation in pulmonary artery pressure (PAP) and then shows a reduction in cardiac output (CO).⁶ The sequence of the hemodynamic improvement after epoprostenol infusion therapy, however, has not been elucidated in detail.

Some patients with PAH improve sufficiently to cease requiring further increases in the epoprostenol dosage (good responders), whereas others (poor responders) still require increasing doses. It is unclear what causes the difference in response to epoprostenol between good and poor responders. Moreover, the hemodynamic changes after ceasing incremental epoprostenol therapy are unclear.

The primary purpose of the present study was to examine the differences in the hemodynamic response to epoprostenol therapy of good and poor responders treated with epoprostenol for 1 or more years. The secondary purpose

was to investigate the hemodynamic course in good responders after cessation of incremental epoprostenol treatment. The third purpose was to clarify whether an increase in CO precedes lowering of the PAP, which reverses the progress in PAH.

Figure 1. Group A consists of patients still continuing to have the dose of epoprostenol increased, whereas Group B patients ceased incremental dosing. BEFORE (thick, white arrows)=immediately before epoprostenol therapy; AFTER (thick, black arrows)=recent data in Group A or immediately before stopping the increase in epoprostenol in Group B; thick, gray arrow=data 1 year after stopping the increasing dose in Group B. Epo, epoprostenol.

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Figure 2. Schema of changes in cardiac output (CO) and mean pulmonary artery pressure (PAP) in cases of pulmonary artery hypertension (PAH), and the hemodynamic change in our hypothesis. (A) Time course of CO and mean PAP during progression of PAH. Stage I=preclinical stage, Stage II=symptomatic/stable stage, Stage III=progressive/declining stage. (Reproduced with permission from Rich S, *Prog Cardiovasc Dis* 1998; **31**: 205–238⁵.) (B) Our hypothesis of hemodynamic improvement with epoprostenol. (C) If our hypothesis is correct, placement in the mean PAP-CO plane moves to 1 of 3 possible points (filled circles) by improvement. (D) In cases of a reduction in mean PAP and increase in CO, most conditions during the improvement (gray circles) may be positioned upwards to the right of the thick arrow. See text for details. Percentage total pulmonary resistance (%TPR) is expressed as a slope in these planes.

Methods

Subjects

After the endothelin receptor blocker, bosentan, was covered under the Japanese health insurance policy, the number of cases of combined therapy with epoprostenol and bosentan increased. Our aim was to elucidate the hemodynamic effect of epoprostenol alone, so we used data from before the use of bosentan was approved under the health insurance policy (ie, before June 2005). Therefore, none of the subjects in the present study had used bosentan or the phosphodiesterase-5 inhibitor, sildenafil. Furthermore, we excluded patients under 15 years of age or end-stage cases referred for lung transplantation. In total, 32 patients, 8 males and 24 females with a mean age of 35.8 ± 15.9 year, fulfilled the criteria and comprised 24 cases of idiopathic heart disease, 5 associated with collagen vascular disease, and 1 case each of congenital heart disease (shunt was closed by surgical operation), portal hypertension, and hereditary hemorrhagic telangiectasia.

Measurements

Catheter examination was performed before the use of epoprostenol, at 3 and 6 months thereafter, and then every

year after the start of epoprostenol infusion, for as long as possible. Of the 32 patients, 8 died within 1 year of starting epoprostenol therapy and the remaining 24 patients were alive after 1 year or more. We selected patients in whom incremental epoprostenol therapy was stopped after satisfying at least 2 of the following criteria: (1) more than three consecutive B-type natriuretic peptide (BNP) levels <50 pg/ml; (2) cardiac index (CI) $>3.00 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$; (3) mean right atrial pressure (RAP) <7 mmHg. The 24 patients who were treated for 1 or more years were divided into 2 groups: group A still required an increase in the dose of epoprostenol (38.7 ± 16.6 years; duration of disease 2.5 ± 1.2 years), and group B did not require further increases (35.2 ± 12.2 years; duration of disease 5.1 ± 2.2 years). One patient in Group A could not undergo catheter examination 1 year or more after starting epoprostenol therapy. Epoprostenol improved the patient's condition sufficiently enough to stop increasing the dose of epoprostenol in 11 cases, but 2 of those patients could not undergo catheter examination 1 year after stopping the incremental dosing. The hemodynamic data associated with acute deterioration from bacteremia or hyperthyroidism after starting epoprostenol therapy were not included in the present study.

In Group A we compared the data obtained immediately

Table 1. Hemodynamics Immediately Before Epo Therapy

	Dead (n=8)	Alive (n=24)	P value
RAP (mmHg)	10.5±7.3	8.5±5.7*	0.39
Mean PAP (mmHg)	67±18	64±12	0.95
PAWP (mmHg)	7.3±4.3	7.2±2.5**	0.50
Mean AoP (mmHg)	95±16	84±14	0.15
Cardiac index (L·min ⁻¹ ·m ⁻²)	1.58±0.28	2.11±0.47	0.001
PVR (Unit)	26.8±7.6	19.0±4.6**	0.01
TPR (Unit)	30.0±8.1	20.9±5.2	0.005
SVR (Unit)	39.3±16.2	25.0±7.0*	0.005
TSR (Unit)	44.2±17.2	27.5±8.0	0.002
PVR/SVR	0.72±0.19	0.76±0.14**	0.70
TPR/TSR	0.71±0.17	0.78±0.17	0.48
BNP (pg/ml)	801±688	454±381*	0.28

*n=23; **n=22.

Epo, epoprostenol; Dead, patients who died within 1 year of starting Epo therapy; Alive, patients who survived 1 year or more; RAP, mean right atrial pressure; PAP, pulmonary artery pressure; PAWP, mean pulmonary artery wedge pressure; AoP, aortic pressure; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance; SVR, systemic vascular resistance; TSR, total systemic resistance; BNP, B-type natriuretic peptide.

Table 2. Paired Comparison of Hemodynamics Between BEFORE and AFTER (n=23)

	BEFORE	AFTER	P value
RAP (mmHg)*	7.5±3.8	6.9±3.4	0.61
Mean PAP (mmHg)	64±12	49±12	<0.0001
PAWP (mmHg)**	7.1±2.5	9.2±2.4	0.005
Mean AoP (mmHg)	83±13	79±13	0.29
PAWP-RAP (mmHg)**	-0.6±3.5	2.3±2.0	0.005
Cardiac index (L·min ⁻¹ ·m ⁻²)	2.10±0.47	3.17±0.72	<0.0001
PVR (Unit)**	19.4±4.5	9.1±3.7	<0.0001
TPR (Unit)	21.1±5.1	10.8±4.2	<0.0001
SVR (Unit)*	25.3±7.0	16.0±5.3	<0.0001
TSR (Unit)	27.6±8.2	17.3±5.6	<0.0001
PVR/SVR**	0.77±0.14	0.57±0.21	0.003
TPR/TSR	0.79±0.16	0.63±0.18	0.003
BNP (pg/ml)*	450±390	240±414	0.03

*n=22; **n=21.

AFTER, recent data in Group A or immediately before stopping increase in Epo in Group B; Group A, patients still continuing Epo (Epo); Group B, patients stopping increase in dose of Epo. See Table 1 for other abbreviations.

before epoprostenol therapy (BEFORE: **Figure 1**) with the recent data (ie, data from immediately before stopping the increment in the dose of epoprostenol in Group B (AFTER: **Figure 1**)). In Group B catheter examination was not performed within 2 weeks of the dose of epoprostenol being increased (ie, AFTER) and then the data from AFTER were compared with data from 1 year after stopping further increases in the dose (**Figure 1**).

More than 20% decrease in the mean PAP or more than 20% increase in CO was defined as a significant change. Resistances were calculated as follows:

$$PVR = \frac{\text{meanPAP} - \text{PAWP}}{\text{CO}} \quad (1)$$

$$TPR = \frac{\text{meanPAP}}{\text{CO}} \quad (2)$$

$$SVR = \frac{\text{meanAoP} - \text{meanRAP}}{\text{CO}} \quad (3)$$

$$TSR = \frac{\text{meanAoP}}{\text{CO}} \quad (4)$$

where PVR is pulmonary vascular resistance (Unit), PAP is pulmonary artery pressure (mmHg), PAWP is pulmonary artery wedge pressure (mmHg), CO is cardiac output (L/min), TPR is total pulmonary resistance (Unit), SVR is systemic vascular resistance (Unit), AoP is aortic pressure

(mmHg), RAP is right atrial pressure (mmHg), and TSR is total systemic resistance (Unit).

Hypothesis of the Hemodynamic Improvement by Epoprostenol

PAH progresses early with an elevation in PAP and later with a reduction in CO (**Figure 2A**); which indicates that the hemodynamics change as PAH advances (represented by the solid line in the mean PAP-CO plane, **Figure 2B**). We also hypothesized that during the hemodynamic improvement with chronic epoprostenol therapy, the change in the hemodynamics was followed by a reversal (shown by a broken line in **Figure 2B**). In other words, hemodynamic improvement appears first as an increase in the CO and then as a reduction in the mean PAP. If this hypothesis is correct, improvement is shown by the mean PAP-CO plane moving to 1 of 3 possible points (filled circles in **Figure 2C**). Moreover, in cases of a reduction in mean PAP and an increase in CO, most conditions during the improvement (shown as gray circles in **Figure 2D**) will be positioned upwards to the right (in contrast with the thick arrow in **Figure 2D**).

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, IL, USA). Non-ordinal categorical data

Table 3. Hemodynamics at AFTER

	Group A (n=12)	Group B (n=11)	P value
Period of Epo usage (days)	703±325	940±489	0.34
Dose of Epo ($\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	34.4±19.4	47.3±17.7	0.11
RAP (mmHg)	8.2±4.0	5.4±1.4	0.09
Mean PAP (mmHg)	55±10	41±8	0.001
PAWP (mmHg)	9.8±2.6*	8.8±2.2	0.40
Mean AoP (mmHg)	78±14	81±12	0.83
PAWP-RAP (mmHg)	1.6±2.2*	3.5±1.7	0.03
Cardiac index ($\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	2.95±0.77	3.42±0.59	0.07
PVR (Unit)	12.4±4.5*	6.3±1.9	0.0001
TPR (Unit)	14.2±5.3	8.0±1.8	0.001
SVR (Unit)	17.0±7.0	14.4±2.1	0.98
TSR (Unit)	19.1±7.2	15.5±2.2	0.38
PVR/SVR	0.72±0.17*	0.45±0.14	0.001
TPR/TSR	0.75±0.14	0.52±0.13	0.001
% change in mean PAP (%)	-10.4±9.4	-35.0±15.1	0.001
% change in cardiac index (%)	33.1±38.8	85.0±46.6	0.004
% change in TPR (%)	-31.2±16.5	-62.7±13.0	<0.0001
% change in TPR/TSR (%)	-0.9±19.5	-34.5±18.3	0.001
BNP (pg/ml)	402±512	36±43	0.009

*n=11.

% change, percent change from BEFORE. See Tables 1,2 for other abbreviations.

Figure 3. Hemodynamics at AFTER on mean pulmonary artery pressure (mPAP)-cardiac output (CO) plane (A) and total pulmonary resistance (TPR)-total systemic resistance (TSR) plane (B). See text for details.

were analyzed using Fisher's exact test. Signed Wilcoxon's rank sum test and Mann-Whitney's U test were used for comparison of paired and unpaired continuous variable data, respectively. Multiple linear regression analysis was performed and explanatory variables in the analysis were selected using backward elimination. All significant tests were 2-tailed. Continuous variables are expressed as mean $\pm$ standard deviation.

Results

Hemodynamic Immediately Before Epoprostenol Infusion Therapy (Table 1)

Compared with patients surviving 1 year or more, those who died within 1 year of starting epoprostenol therapy had a low CI and high TPR. There was no difference in the mean RAP of dead patients and survivors at 1 year after starting epoprostenol therapy. In total, 4 of 9 patients with RAP=12 mmHg or more died, and 4 of 22 patients with RAP<12 mmHg died ($P=0.19$).

Hemodynamic After Epoprostenol Therapy (Comparison Between BEFORE and AFTER) (Table 2)

Mean PAP was low, and the PWP minus RAP and the CI were high at AFTER compared with BEFORE. Both TPR and TPR/TSR were low.

Mean PAWP minus mean RAP increased from -1.2 ± 4.4 mmHg to 3.2 ± 1.5 in Group B ($P=0.02$), but was unchanged in Group A (-0.1 ± 2.5 mmHg vs 1.6 ± 2.2 ; $P=0.17$).

Hemodynamic Pulmonary Selectivity (Hemodynamics at AFTER) (Table 3)

In Group B, the CI tended to be high, whereas the mean PAP, TPR and TPR/TSR were low compared with Group A (Table 3, Figure 3). Moreover, the mean PAWP minus the mean RAP was high.

When data at BEFORE were expressed as 100%, the percentage change in the CI at AFTER was high and the percentage changes in the mean PAP, TPR and TPR/TSR were more negative in Group B than in Group A.

Changes in the CI, TPR, TPR/TSR and mean PAWP minus mean RAP were defined as explanatory variables, and the predictors of the change in PAP from BEFORE to

Figure 4. Hemodynamics in individual cases at AFTER (A) and hemodynamic changes under increasing epoprostenol (B and C). Plots in both Panels B and C indicate hemodynamics under an increasing dose of epoprostenol. Individual changes in Panel B are shown by thin, solid arrows. (B) Cases in Zone III at AFTER. (C) Cases in Zone I, II or IV at AFTER. Most conditions during the improvement in patients in Zone II at AFTER were positioned between 80 and 120 in the percentage mean pulmonary artery pressure (mPAP). See text for details. CO, cardiac output; CI, cardiac index; TPR, total pulmonary resistance.

AFTER were analyzed using multiple regression analysis with backward elimination. Only changes in TPR and mean PAWP minus mean RAP were significant ($P=0.03$ and 0.002 , respectively).

Changing Pattern of Hemodynamics Induced by Increasing Dose of Epoprostenol

Data obtained immediately before epoprostenol therapy in individual cases were expressed as 100% and shown in Figure 4A. Zone I is where both the percentage mean PAP (%mPAP) and percentage CO (%CO) are between 80% and 120% (3 cases), zone II is where %mPAP is between 80% and 120%, and %CO is more than 120 (9 cases), zone III is where %mPAP is less than 80% and %CO is more than 120% (10 cases), and zone IV is where %mPAP is less than 80% and %CO is between 80 and 120% (1 case). TPR decreased more than 20% at AFTER in 20 of 23 cases; 9 of 11 patients in Group B and 1 of 12 in Group A were located in zone III ($P=0.001$).

In order to change the data for cases in zone III (Figure

4A) to resemble those shown in Figure 2, the mean PAP at BEFORE was displayed as 100%, and that at AFTER as 0% (Figure 4B). CO at BEFORE was displayed as 0%, and that at AFTER as 100%. Pooled data of the hemodynamic changes under increasing epoprostenol dose are shown as circles in Figure 4, which are scattered evenly upwards to the right and downwards to the left forming a solid arrow ($P=0.38$). Thus, our hypothesis that hemodynamic improvement with epoprostenol therapy results from an increase in CO first, and then from a reduction in PAP was refuted.

Data for the patients in zones I, II and IV (Figure 4A) at BEFORE were expressed as 100% in Figure 4C as in Figure 4A. All values in Figure 4C were obtained during increasing epoprostenol dosing. The %mPAP during the improvement of patients in Zone II at AFTER was between 80% and 120%.

The percentage change from BEFORE to AFTER in both PVR/SVR and TPR/TSR was more negative in patients in Zone III compared with those in other zones ($-9.2 \pm 22.0\%$ vs $-43.7 \pm 27.0\%$, $P=0.002$; $-6.2 \pm 18.7\%$ vs $-34.2 \pm 25.1\%$, $P=0.0002$, respectively).

Table 4. Hemodynamic Effect of Termination of the Increase in Epo Therapy (n=9)

	Immediately before termination	1 year after termination	P value
RAP (mmHg)	5.0±1.1	5.3±2.0	0.73
Mean PAP (mmHg)	42±8	37±9	0.02
PAWP (mmHg)	8.1±1.5	8.6±2.2	0.40
Mean AoP (mmHg)	80±11	80±6	0.77
Cardiac index (L·min ⁻¹ ·m ⁻²)	3.29±0.57	3.18±0.49	0.44
PVR (Unit)	6.8±1.7	6.0±2.0	0.03
TPR (Unit)	8.3±1.7	7.7±2.1	0.09
SVR (Unit)	11.7±1.8	15.7±2.4	0.31
TSR (Unit)	15.7±1.9	16.7±2.3	0.31
PVR/SVR	0.46±0.12	0.38±0.11	0.03
TPR/TSR	0.54±0.11	0.48±0.11	0.049
BNP (pg/ml)	35.9±43.0	16.3±23.0	0.02

See Table 1 for abbreviations.

The first catheter data after epoprostenol therapy showed 4 cases with positioning upwards to the right of the thick broken arrow shown in **Figure 4B** (up-rightward cases), 5 positioned down to the left (down-left cases), and 1 on the arrow. Before epoprostenol, the CI was $1.96 \pm 0.49 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ in the up-rightward cases and 1.96 ± 0.55 in the down-left cases ($P=1.00$), and mean PAP was $62 \pm 4 \text{ mmHg}$ in the up-rightward cases and 66 ± 1 in the down-left cases ($P=0.19$).

Hemodynamics at 1 Year After Stopping the Increasing Dose of Epoprostenol (Table 4)

CO was unchanged, and mean PAP slightly decreased, compared with AFTER. TPR tended to decrease, and both PVR and TPR/TSR decreased.

Discussion

Predictors of Mortality Within 1 Year of Epoprostenol Therapy

In the present study, deaths within 1 year of starting epoprostenol therapy were related to low CO and high TPR. Mortality was high, but not significant, in patients with mean RAP > 12 mmHg. Poor prognostic predictors when epoprostenol could not be used clinically were elevation of the RAP and PAP, and low CO.⁷ In a recent report, poor prognostic predictors were high RAP and poor vasodilatory response to adenosine at baseline,³ and in another report the predictors were high RAP and low PAP at baseline.⁴

Hemodynamic Changes After Epoprostenol Therapy

Patients surviving more than 1 year after the start of epoprostenol therapy, with clinical improvement because of a good response to epoprostenol and cessation of the increase in the dose of epoprostenol (Group B), had a greater reduction in mean PAP, TPR and TPR/TSR, and a greater increment in CO than patients who were unable to cease the incremental therapy (Group A). These findings suggest that patients in Group B had greater pulmonary sensitivity to epoprostenol. Moreover, the increment of the mean PAWP minus the mean RAP by epoprostenol therapy in Group B indicates that the volume that had shifted to the right-sided heart because of PAH had returned to the left-sided heart.

One therapeutic target in PAH is to reduce the mean PAP. Important predictors for achieving that target with epoprostenol therapy in the present study were not only a reduction in TPR, but also the volume-return to the left-sided heart via the pulmonary circulation.

Changing Pattern of Hemodynamics While Increasing the Dose of Epoprostenol

PAH progresses early with an elevation in PAP and later with a reduction in CO,⁶ but it is unknown whether the hemodynamic improvement reverses the course of PAH progression (ie, CO increases first, and then PAP reduces). If this is correct, in patients with both an increase in CO and a reduction in the mean PAP with epoprostenol therapy, most conditions during the improvement (gray circles) may be positioned upwards to the right along the thick arrow in **Figure 2D**. Nevertheless, as shown in **Figure 4B**, these circles scattered evenly upwards to the right and downwards to the left forming the right downward solid arrow, which means that when the mean PAP was reduced by epoprostenol therapy, there was an accompanying increase in CO. One reason for this may be that the right ventricular hypertrophied heart ejects a disproportionately large amount of blood to the pulmonary vasculature. Another reason may be hemodynamic. When there is no obvious shunt, the definitions of TPR and TSR induce the following equations:

$$\frac{\text{meanPAP}}{\text{TPR}} = \text{CO} = \frac{\text{meanAoP}}{\text{TSR}} \quad (5)$$

$$\frac{\text{TPR}}{\text{TSR}} = \frac{\text{meanPAP}}{\text{meanAoP}} \quad (6)$$

Mean AoP is low in patients with PAH. Under the condition of constant mean AoP (no excessive lowering of mean AoP) after epoprostenol therapy, mean PAP is unchanged in patients with no pulmonary selectivity to epoprostenol (no change in TPR/TSR) by equation (6). On the other hand, mean PAP falls in patients with pulmonary selectivity to epoprostenol (decrease in TPR/TSR) by equation (6). CO increases in both cases by (5), because TSR decreases and mean AoP is unchanged. These results imply that drugs dilating the systemic vasculature are associated with an increase in CO, when mean AoP is kept constant. The CI or mean PAP before epoprostenol therapy did not affect whether the hemodynamic data under increasing epoprostenol dosing were positioned upper right or lower left of the thick broken arrow in **Figure 4B**.

Our results show that in patients improving more than 20% in TPR, 10 improved more than 20% in both CO and mean PAP, 9 cases improved more than 20% in CO only, and 1 case improved more than 20% in mean PAP only (**Figure 4A**). That is to say, most cases with an improvement in TPR by epoprostenol also had an improvement in CO, which indicates that a reduction in the mean PAP

without an increase in CO cannot be expected.

In some cases the dose of epoprostenol has to be increased continuously because of insufficient reduction in the mean PAP. Our results show that patients without pulmonary vascular selectivity to epoprostenol cannot achieve significant reductions in the mean PAP, so require additional medication to reduce it.

Hemodynamics at 1 Year after Stopping Increasing the Dose of Epoprostenol

Many physicians and patients are apprehensive that stopping the incremental dosing of epoprostenol will lead to a deterioration in the patient's hemodynamics. In the present study, however, the hemodynamics did not deteriorate, but the mean PAP, PVR and PVR/SVR further decreased. Using stable doses of epoprostenol our patients showed no signs of tachyphylaxis to epoprostenol, as was thought to be the case previously.⁸ When epoprostenol is acutely loaded in patients with PAH, the vasodilatory effect is stronger in the systemic vasculature than in the pulmonary vasculature.^{8,9} Pulmonary selectivity appears in the chronic phase,^{8,10} which suggests that, also for some time after increasing the dose in chronic use, the vasodilatory effect is stronger in the systemic vasculature than in the pulmonary vasculature. No tachyphylaxis against epoprostenol and the development of pulmonary selectivity may contribute to the hemodynamic improvement observed even after stopping the incremental dosing of epoprostenol.

Study Limitations

Epoprostenol therapy was approved by the Japanese government in 1999, so the present patients received the therapy for less than 10 years, which may not be sufficient to access the hemodynamic time course; however, it was very difficult to assess the effects of epoprostenol alone over a longer term after the endothelin receptor blocker, bosentan, was approved. Second-line bosentan therapy was indicated in poor responders, and bosentan was also added even for good responders to reduce the dose of epoprostenol.

Conclusion

In good responders, pulmonary selectivity to epopro-

stenol was high, and the blood returning to the left-sided heart via the pulmonary circulation increased. Hemodynamics were further improved even after cessation of the incremental dosing of epoprostenol. Our data did not show that an increase in CO preceded lowering of PAP over the time course of improvement.

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