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ORIGINAL ARTICLE

New strategy to resume and taper epoprostenol after lung transplant for pulmonary hypertension

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Abstract

Objective The perioperative outcome of lung transplantation (LTx) for patients with severe pulmonary hypertension (PH) remains poor due to the occurrence of primary graft dysfunction (PGD) from left ventricular failure. We hypothesized that tapering pretransplant use of epoprostenol rather than abrupt discontinuation after transplantation might improve perioperative outcomes.

Methods We performed 23 LTxs for patients with severe PH who received epoprostenol therapy from 2008 until 2021. In the discontinued group ($n=6$), epoprostenol was discontinued after the establishment of extracorporeal circulation. In the tapered group ($n=17$), epoprostenol was discontinued and resumed after reperfusion, and then gradually tapered over the following 2 weeks. We assessed survival, bleeding, blood transfusion, re-opening of the chest, oxygenation, PGD score, extracorporeal membrane oxygenation (ECMO) requirement for recovery after transplantation, and duration of mechanical ventilation.

Results The PGD score was significantly lower in the tapered group than in the discontinued group at 0 h, 24 h, and 48 h after LTx. In addition, the discontinued group required longer mechanical ventilation than the tapered group. Delayed chest closure and post-transplant ECMO use for recovery occurred significantly more frequently in the discontinued group.

Conclusions To resume and taper epoprostenol administration after reperfusion in patients with severe PH may be a valuable new strategy associated with better perioperative outcomes.

Keywords Pulmonary hypertension · Lung transplantation · Epoprostenol · Prostacyclin

Introduction

Due to the effective use of various medical therapies for pulmonary arterial hypertension (PAH), lung transplantation (LTx) is performed less frequently for patients with severe pulmonary hypertension (PH); however, it remains an important treatment option for patients who are failing maximal medical therapy. Historically, the early postoperative mortality for patients undergoing LTx for PAH was higher than it was for those with most other end-stage lung diseases due to the occurrence of early graft dysfunction [1]. However, the main cause of primary graft dysfunction (PGD) in these patients was left ventricular failure, rather than residual PH [2]. In addition, Porteous et al. found that differences in left ventricular diastolic function may contribute to the development of PGD [3].

A treatment algorithm for PAH was provided in the 2015 European Society of Cardiology and European Respiratory Society guidelines; the guidelines also indicated

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that high-risk patients (WHO-FC IV) are recommended to receive initial combination therapy, which includes intravenous prostacyclin [4]. Presently, pretransplant use of epoprostenol is prevalent for patients with end-stage PH; however, it is generally discontinued at the time of transplantation. In our early experience with LTxs for PH, we often encountered severe PGD. We theorized that abrupt discontinuation of epoprostenol might be a contributing factor for PGD; therefore, we changed our epoprostenol strategy from abrupt discontinuation to tapering by the end of 2013. This study aimed to compare the effect of abrupt epoprostenol discontinuation with that of epoprostenol tapering therapy on early outcomes after LTx for PH.

Patients and methods

In this retrospective study, the patient chart reviews were performed using an electronic medical record system. This study was approved by Kyoto University's Institutional Review Board. We performed 266 LTxs from June 2008 to June 2021, and 23 patients with PH were administered epoprostenol (10–200 ng/kg/min) therapy. These patients were allocated into two groups: a discontinued group ($n=6$) and a tapered group ($n=17$). For the patients in the discontinued group, epoprostenol was discontinued after extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB). For the patients in the tapered group, epoprostenol was discontinued just as it was with the discontinued group; however, after reperfusion, it was resumed at one-quarter of the preoperative dose. It was then gradually tapered over the next 2 weeks according to the patient's heart function, as shown on echocardiography. Catecholamine was also tapered along with the epoprostenol. We assessed survival, intra- and postoperative bleeding, blood transfusions, chest re-opening for postoperative bleeding or hematoma, the PaO_2/FiO_2 (P/F) ratio, PGD scores after transplantation, the ECMO requirement for recovery after transplantation, delayed chest closure frequency, mechanical ventilation duration, pulmonary artery (PA) catheter insertion, and intensive care unit stay. We compared the data for all 23 patients in the two groups, as well as just among the nine patients who underwent CPB since the tapered group had more recent ECMO cases.

Statistical analysis

All the statistical analyses were performed using STATVIEW v5.0 (Abacus Concepts, Inc., Berkeley, CA, USA). The values are expressed as the mean ± standard deviation. We used the Fisher's exact test and Mann–Whitney *U* test to explore the differences in the patients' backgrounds and clinical data between the groups, respectively. Statistical significance was set at $p<0.05$.

Results

Patient characteristics

The patient characteristics are shown in Table 1. Four of the six patients in the discontinued group had idiopathic PAH (IPAH), and the remaining patients had pulmonary veno-occlusive disease and residual PH after the correction of the transposition of the great arteries. Conversely, 16 of the 17 patients in the tapered group had IPAH; three of them also had atrial septal defect, pulmonary arteriovenous malformation, and giant PA.

Table 1 Patient characteristics and operative procedures

Group	Discontinued ($n=6$)	Tapered ($n=17$)	*p value
Sex (F:M)	6:0	13:4	
Underlying diseases	IPAH 4 PVOD 1 TGA post-correction 1	IPAH 16 including IPAH + ASD, 1; IPAH + AVM, 1; IPAH + giant PA, 1 Secondary PH due to systemic sclerosis 1	
Operative procedure			
LDLLTx:CLTx	4:2	3:14	0.045
Single:double	2:4	1:16	0.16
CPB:ECMO	5:1	4:13	0.018

IPAH idiopathic pulmonary arterial hypertension, *PVOD* pulmonary veno-occlusive disease, *ASD* atrial septal defect, *AVM* arteriovenous malformations, *TGA* transposition of the great arteries, *LDLLTx* living-donor lobar lung transplantation, *CLTx* cadaveric lung transplantation, *CPB* cardiopulmonary bypass, *ECMO* extracorporeal membrane oxygenation

*p values are for the differences between groups by Fisher's exact test

Operative procedure

The operative procedures are summarized in Table 1. Four of the six patients in the discontinued group received living-donor lobar LTx (LDLLTx), and the others received cadaveric LTx (CLTx). A total of 14 of the 17 patients in the tapered group received CLTx. Although double LTx is usually performed for patients with PH, two pediatric patients in the discontinued group and one adult in the tapered group underwent single LTx. An adult single lobe was considered large enough for the two pediatric patients, while the adult patient, who was suffering from secondary PH due to systemic sclerosis, was thought to be controllable with a single LTx.

Recently, an increasing number of transplant centers have changed their extracorporeal circulation (ECC) strategies from CPB to ECMO [5]. Our center also changed our ECC strategy in 2013; since then, we have predominantly used ECMO, although CPB is still mandatory in some cases, such as when the patient requires concomitant intracardiac repair or vasculoplasty for a giant pulmonary trunk, or when single lung ventilation is difficult, especially with pediatric patients. In the current study, there were significantly more ECMO cases in the tapered group; therefore, we compared the data for all the patients in the two groups, as well as for only the patients who underwent CPB.

Bleeding and requirement of blood products

The intra- and postoperative outcome results are shown in Table 2. There were no significant differences in the intra- and postoperative bleeding volumes within 24 h posttransplant between the groups, even among only the CPB cases. The discontinued group had significantly more

Table 2 Intra- and postoperative outcomes

Comparison group	All cases			Only CPB cases		
	Discontinued ($n=6$)	Tapered ($n=17$)	p value	Discontinued ($n=5$)	Tapered ($n=4$)	*p-value
Bleeding						
Intraoperative bleeding (mL)	3628 ± 3390	3247 ± 3102	0.65	3904 ± 3714	6248 ± 5261	0.73
Postoperative bleeding within 24 h	2742 ± 2329	1287 ± 814	0.22	2329 ± 2345	1835 ± 1336	1.00
Re-thoracotomy for postoperative bleeding (yes/no)	0.52	4/2	2/15	0.021	3/2	1/3
Blood transfusion						
Intraoperative RBC transfusion (units)	8 ± 4	7 ± 8	0.29	8 ± 4	12 ± 13	0.90
Postoperative RBC transfusion within 7 days	20 ± 18	6 ± 6	0.074	17 ± 18	9 ± 8	0.56
Intraoperative PC transfusion	35 ± 12	25 ± 15	0.082	36 ± 13	33 ± 22	0.71
Postoperative PC transfusion within 7 days	39 ± 31	6 ± 10	0.0046	36 ± 34	5 ± 10	0.095
Oxygenation						
P/F ratio 0 h after LTx	213 ± 164	222 ± 125	0.81	188 ± 192	318 ± 166	0.63
P/F ratio 24 h after LTx	281 ± 143	290 ± 86	0.89	293 ± 173	317 ± 126	1.00
P/F ratio 48 h after LTx	238 ± 25	263 ± 64	0.48	225 ± 14	288 ± 101	0.31
P/F ratio 72 h after LTx	286 ± 108	287 ± 68	0.90	326 ± 68	323 ± 41	1.00
PGD score						
PGD score 0 h after LTx	2.2 ± 1.3	0.9 ± 1.4	0.049	2.0 ± 1.4	0.8 ± 1.5	0.23
PGD score 24 h after LTx	2.0 ± 1.5	0.6 ± 1.1	0.034	1.8 ± 1.6	0.5 ± 1.0	0.034
PGD score 48 h after LTx	1.8 ± 1.5	0.4 ± 0.9	0.018	1.8 ± 1.6	0	0.018
PGD score 72 h after LTx	1.0 ± 1.5	0.2 ± 0.7	0.19	0.6 ± 1.3	0	0.19
Delayed chest closure (yes/no)	5/1	3/14	0.0086	4/1	1/3	0.21
Posttransplant ECMO use for recovery (yes/no)	5/1	2/15	0.0034	4/1	1/3	0.21
Duration of mechanical ventilation after LTx	42 ± 42	15 ± 8	0.023	47 ± 44	14 ± 9	0.049
Duration of PA catheter insertion	3.8 ± 2.3	1.9 ± 1.4	0.072	4.0 ± 2.6	2.7 ± 2.1	0.59
Hospital death (yes/no)	1/5	0/17	0.26	1/4	0/4	1.00

CPB cardiopulmonary bypass, *RBC* red blood cell, *LTx* lung transplantation, *P/F ratio* PaO_2/FiO_2 ratio, *PGD* primary graft dysfunction, *ECMO* extracorporeal membrane oxygenation

*p values are for the differences between groups by Fisher's exact test and the Mann–Whitney test

re-thoracotomies for postoperative bleeding; however, there were no significant differences between the groups if the comparison was limited to the CPB cases. The requirement for intraoperative red blood cell (RBC) and platelet concentrate (PC) transfusions did not differ significantly between the groups. Postoperative RBC transfusions were required more frequently for the patients in the discontinued group, although the difference was not significant; however, postoperative PC transfusions were required significantly more frequently for the patients in the discontinued group.

P/F ratio and PGD score

The P/F ratio did not show any significant differences between the groups at any time after the LTxs; however, the PGD score was significantly lower for the tapered group than it was for the discontinued group at 0, 24, and 48 h after the LTxs. It was even lower for the tapered group when the comparison was limited to the CPB cases at 24 h and 48 h after the LTxs. Therefore, the patients in the discontinued group required longer mechanical ventilation than those in the tapered group when all the patients were compared, as well as when only the CPB patients were compared. Delayed chest closure and post-transplant ECMO use for recovery occurred significantly more frequently in the discontinued group when the comparison was made among all the patients.

Survival

One patient in the discontinued group died on day 125 due to multiple organ failure, and two patients in the tapered group died (one on day 949 and another on day 1135) due to chronic lung allograft dysfunction. The 1-, 3-, and 5-year overall survival rates were 83, 83, and 83% for the discontinued group and 100, 92, and 83% for the tapered group, respectively.

Discussion

In this study, we compared two epoprostenol discontinuation strategies for patients with PH: abrupt discontinuation during transplant surgery and resumption before reperfusion with gradual tapering according to heart function. We found that the PGD score was significantly lower for the tapered group than for the discontinued group, and the mechanical ventilation duration was significantly shorter for the tapered group than for the discontinued group. Therefore, we believe that posttransplant use of epoprostenol may contribute to the maintenance of left heart function and prevention of pulmonary edema.

Severe PH is associated with a higher risk of posttransplant PGD [6, 7]. Porteous et al. investigated the risk factors for PGD in patients with PH and found that the mean PA pressure, recipient body mass index, donor smoking, reperfusion FiO_2, and CPB use were similar between the patients with PH and those in the overall LTx group. Furthermore, right atrial pressure and creatinine were also risk factors that had not previously been identified; these risk factors may reflect decompensated left ventricular and/or right ventricular systolic or diastolic function with poor tissue perfusion [8]. Hoeper et al. indicated that a better understanding of the pathophysiological changes that occur after transplantation for PH, combined with the adaptation of therapeutic strategies (e.g., achieving a negative fluid balance, including the use of hemofiltration, as necessary, extended ECMO support), substantially reduces the occurrence of early graft dysfunction [9]. Tudorache et al. reported that postoperative prolongation of veno-arterial ECMO after transplantation effectively prevents PGD [10]. Toyooka et al. reported that right ventricular function recovery occurred early after LTx for the patients in the PH group, while left ventricular function recovery required more than 6 months [11]. Avriel et al. also reported that the main cause of primary graft dysfunction in these patients was left ventricular failure, rather than residual PH [2]. In the early postoperative period after an LTx for patients with severe PH, a small left ventricle with a thin myocardium due to a long-standing underfilling bloodstream that is compressed by the hypertrophic right ventricle develops diastolic dysfunction. The left ventricle is unable to accommodate the normalized preload after reperfusion, resulting in pulmonary edema due to an elevated filling pressure in the left ventricle. In this situation, the postoperative use of veno-arterial ECMO could provide time for the left ventricle to gradually adapt to the altered hemodynamics [10]. Oida et al. demonstrated that the prostacyclin receptor is expressed in various organs, including the thymus, spleen, and neurons, and it is expressed ubiquitously by the smooth muscle cells in arteries of various sizes and in a variety of organs [12]. Therefore, in our strategy, epoprostenol may play an important role in dilating systemic arteries and decreasing vascular resistance to alleviate afterload in long-standing thinned left ventricles with decreased systolic dysfunction. This means that epoprostenol tapering therapy after reperfusion may be a reasonable strategy to rescue left ventricular dysfunction. In addition, prostacyclin has been reported to have a protective effect against vascular leakage in lung ischemia–reperfusion [13], which is consistent with our findings.

Oida et al. also demonstrated that the prostacyclin receptor is highly expressed in PA smooth muscle cells [12]. Falcetti et al. reported that prostacyclin receptor expression in PA smooth muscle cells of intra-acinar arteries was significantly weaker in treated IPAH samples than it was in

untreated samples [14]. We assume that prostacyclin receptor expression in pretransplant patients with severe IPAH who are receiving epoprostenol therapy is weak. Though whether the combination of reduced prostacyclin receptor expression and abrupt epoprostenol cessation explains the posttransplant left heart failure is unclear, tapering the dose after reperfusion might mitigate the effect of regular dose dependence.

In our transplant program at Kyoto University Hospital, we have applied several strategies for IPAH patients. First, donor grafts in good condition, such as lungs from younger donors without a history of smoking, are typically accepted since the hypertrophic right ventricle associated with prolonged PH requires abundant vascular beds. Functional size matching using forced vital capacity for patients with PH is 50%, especially with LDLLTxs, which is higher than that for patients without PH [15]. Second, we always put posttransplant patients in deep sedation for at least 3 days on mechanical ventilation to prevent left heart failure due to sudden arousal from shallow sedation. Muscle relaxants are required if sedation control is difficult. Furthermore, a tracheostomy is performed for nearly all the patients with PH to prevent agitation caused by orotracheal intubation and enable easier weaning from mechanical ventilation. In our study, all patients in the discontinued group underwent tracheostomy except one with multiple organ failure, and 14 out of 17 (82%) patients in the tapered group underwent tracheostomy. For these patients who underwent tracheostomy, it is possible to eat; however, it takes time to start speaking. Third, right and left ventricle function is monitored more carefully and longer using a Swan–Ganz catheter for pulmonary hemodynamics and a catheter for left atrial pressure, as well as with frequent echocardiography. Fourth, and most importantly, epoprostenol is tapered, along with sufficient catecholamine administration. Prostacyclin receptors exist not only in the PAs but also in the systemic arteries, and epoprostenol is a potent vasodilator of systemic vessels. Catecholamine is essential to increase the cardiac output of thinned left ventricles with reduced cardiac output due to long-standing underfilling caused by elevated pulmonary vascular resistance that cannot tolerate the increased preload after newly implanted lungs, and epoprostenol is important for managing abrupt preload increases. Although not in the context of transplantation, Akagi et al. showed the importance of catecholamine use at the initiation of epoprostenol therapy [16].

The limitations of our study include its retrospective design, sample size, and the fact that it was conducted at a single institution. Additionally, the tapered group had more recent patients who underwent other new perioperative strategies, such as the intraoperative use of ECMO, instead of CPB. Of note, PGD occurred less frequently in the tapered group, even when limited to the CPB cases.

Conclusion

To resume and taper epoprostenol administration after reperfusion in PH patients may be a valuable new strategy that is associated with better perioperative outcomes.

Declarations

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose.

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