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Marked Reduction of Pulmonary Artery Pressure After Registration for Lung Transplantation Is Associated With Long-Term Survival in Patients With Pulmonary Arterial Hypertension

— Cohort Study —

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Background: The waiting period for lung transplantation (LT) is approximately 3 years in Japan. The prognosis of patients with pulmonary arterial hypertension (PAH) awaiting LT is poor without LT. Patients at the present center often survive in the long term after registration for LT. The aim of this study was to elucidate why some patients survive in the long term by investigating changes in pulmonary artery pressure (PAP) after registration, and medication used.

Methods and Results: This study involved 57 patients with PAH who were enrolled in a registry for LT at Okayama University Hospital. We divided patients into 3 groups according to outcome: LT (n=27); death without LT (n=21); and survival without LT (n=9). The median interval from PAH diagnosis to epoprostenol treatment was shorter in the survival group (58 days) than in the LT group (378 days) and death group (545 days). Eight patients in the survival group, 13 in the LT group, and 13 in the death group underwent right heart catheterization after registration. Percent change in mean PAP after registration was significantly greater in the survival group (−32%) than in the LT group (−13%) and death group (1%; P<0.01).

Conclusions: Even after LT registration, patients who received epoprostenol infusion soon after diagnosis of PAH often had marked reduction in PAP and long-term survival without LT.

Key Words: Lung transplantation; Pulmonary artery hypertension; Pulmonary artery pressure; Survival

Pulmonary arterial hypertension (PAH) is characterized by elevation of pulmonary artery pressure (PAP), which leads to right heart failure and death. PAH-specific drugs, such as prostacyclin, endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE5i), soluble guanylate cyclase stimulators, and IP receptor agonists, have been developed over the past 20 years. These medical therapies improve exercise capacity and prognosis in patients with PAH.[1] Patients with World Health Organization functional class III and IV are suitable for lung transplantation (LT).[2]

The waiting period for LT is approximately 3 years in Japan. Waiting list mortality is very high in patients with idiopathic PAH.[3] Therefore, the prognosis of patients on the LT list has been extremely poor unless LT is performed. At the present center, however, some patients on the LT list have survived longer than 10 years. This situation is very rare and could provide useful clinical information, if we can determine the reasons for long-term survival.

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The aim of this study was therefore to elucidate the reasons for long-term survival in PAH patients on the LT list by evaluating their clinical characteristics at LT registration and hemodynamic changes after LT registration in relation to medication used.

Methods

Study Design

The study conformed to the principles outlined in the

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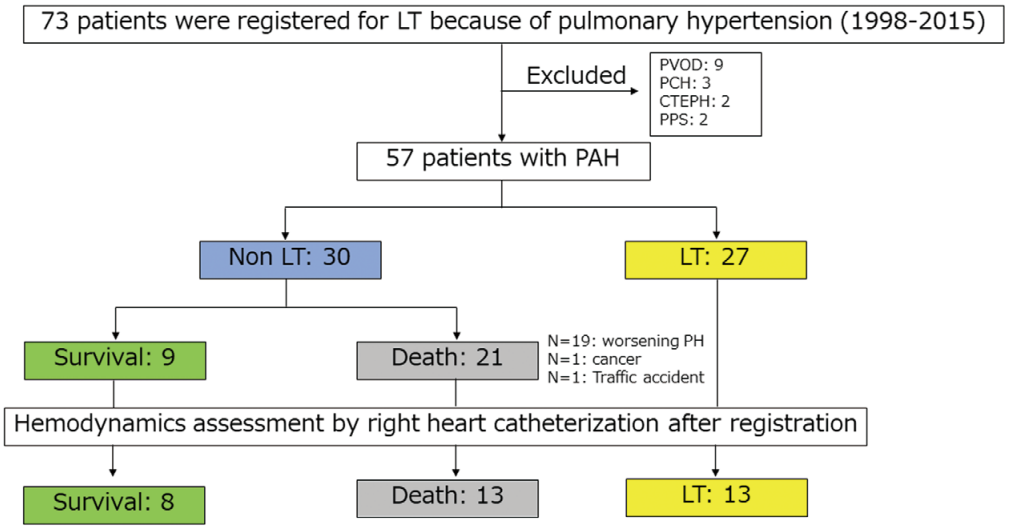

Figure 1. Clinical course. The numbers in the bottom row represent the number of patients who had follow-up data available. Follow-up hemodynamics assessment was done before lung transplantation (LT) in the LT group. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PPS, peripheral pulmonary artery stenosis; PVOD, pulmonary veno-occlusive disease.

Declaration of Helsinki. It was approved by the institutional review board and ethics committees of Okayama University (no. 1909-008). The requirement for informed consent was waived because of the low-risk nature of this retrospective study and the inability to obtain consent directly from all subjects. Instead, we extensively announced this study protocol at Okayama University Hospital and on the website (http://www.hsc.okayama-u.ac.jp/ethics/koukai/jyunkan/index.html) and gave patients the opportunity to withdraw from the study.

Patients

A total of 73 patients with PAH were registered for LT at Okayama University Hospital between 1998 and 2015. Causes of PAH included idiopathic, heritable, congenital heart disease, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, peripheral pulmonary artery stenosis, and chronic thromboembolic pulmonary hypertension. Of these 73 patients, we excluded 9 patients with pulmonary veno-occlusive disease, 3 with pulmonary capillary hemangiomatosis, 2 with chronic thromboembolic pulmonary hypertension, and 2 with pulmonary hypertension associated with peripheral pulmonary artery stenosis.

Diagnosis of PAH

PAH was defined as mean PAP ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance ≥3 Wood units on right heart catheterization (RHC). Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis were diagnosed according to lung pathology in the patients who received LT. Peripheral pulmonary artery stenosis was diagnosed on pulmonary artery angiography. Chronic thromboembolic pulmonary hypertension was diagnosed on lung ventilation/perfusion scan and pulmonary artery angiography. Information on pretreatment with PAH-specific drugs, echocardiography parameters, blood testing, and hemodynamics were obtained from medical records. Postoperative immunosuppression was achieved with triple drug therapy under a previously described protocol.[4]

Criteria for LT Registration

Patients deteriorating on optimal medical therapy need to register for LT because the waiting list period in Japan is very long. Epoprostenol was available in 1999; the first ERA (bosentan) was available in 2005, and the first PDE5i (sildenafil) was available in 2007 in Japan. Therefore, the definition of optimal medical therapy differs according to year of initiation.

Recipient Selection

Patients who require LT are registered with the Japan Organ Transplantation Network. The LAS system and high-priority list have not yet been adopted in Japan. Available cadaveric lungs were allocated to recipients by the Japan Organ Transplant Network according to the waitlist order, lung size, ABO compatibility, and matching of predicted pulmonary function.

Post-LT Registration Outcome

Patients who registered for LT were divided into 2 groups according to transplantation status: LT and non-LT. The LT group consisted of patients who received living donor LT or cadaveric donor LT. In the non-LT group, patients had 2 outcomes: death or survival. The death group was defined as patients who died without LT. The survival group was defined as patients who survived without LT. We defined long-term survival as >10 years after registration for LT.

Primary Endpoint and Analysis

We examined all-cause death and LT in all patients. To assess predictors related to death after registration for LT, we examined the following factors: age at registration, sex,

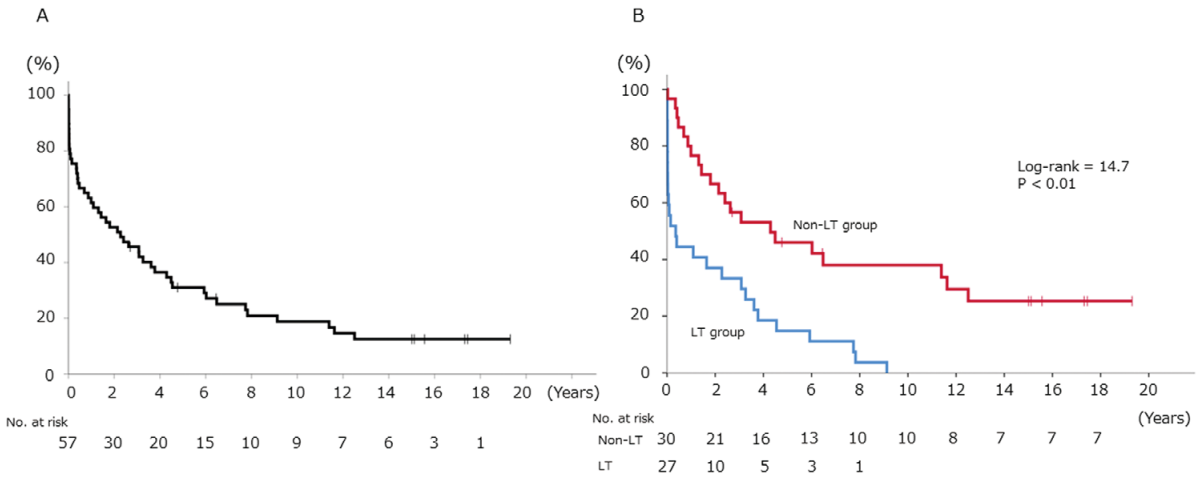

Figure 2. Kaplan-Meier curves for (**A**) death and receipt of LT in the total group and (**B**) for death in the non-lung transplantation (non-LT) group and for receipt of LT in the LT group.

diagnosis, treatment, mean PAP at registration, cardiac index at registration, brain natriuretic peptide (BNP) at registration and percent change in mean PAP.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL, USA). All data are expressed as mean±SD or median (IQR). Continuous variables were compared between groups using the Mann-Whitney U-test or Kruskal-Wallis test for non-normally distributed data, and the unpaired t-test for normally distributed data. Categorical variables were compared using the chi-square test. Kaplan-Meier analysis was used to estimate survival status, and the log-rank test was used to compare survival distribution. Patients were censored if they died while waiting for LT in the non-LT group (survival and death groups). Patients were censored if they received LT in the LT group. The percent change in mean PAP between registration and follow-up was compared in analysis of covariance models, with the baseline mean PAP as the covariate. Cox proportional hazards analysis was used to evaluate factors associated with death after registration. P<0.05 was considered significant.

Results

Clinical Course After LT Registration

Figure 1 shows the patient clinical course. The final study group consisted of 57 patients. The number of patients with idiopathic PAH was 48, the number of patients with heritable PAH was 2, and the number of patients with congenital heart disease was 7. Twenty-seven patients received LT (LT group) and 30 did not (non-LT group; **Supplementary Table 1**). Eighteen patients received a living donor LT and 9 patients received cadaveric LT. In the non-LT group, 9 patients survived and 21 died. **Figure 2A** shows the Kaplan-Meier curve for death and receipt of LT in the entire study group. In the total group, survival was 31.0% at 5 years, 18.8% at 10 years, and 12.5% at 15 years after LT registration. Nineteen patients (90%) in the death group died from worsening pulmonary hypertension. One patient died from cancer and 1 died in a traffic accident. **Figure 2B** shows the Kaplan-Meier curves according to death in the non-LT group and according to receipt of LT in the LT group. Death and transplant-free survival in the non-LT group was 76.7% at 1 year, 46.0% at 5 years, and 38.0% at 10 years after LT registration; and 44.4%, 14.8%, and 0%, respectively, in the LT group (P<0.01, log-rank test). Nine patients had long-term survival after LT registration without receiving LT.

Patient Characteristics

Table 1 lists patient characteristics at LT registration in the 3 groups. All patients were classified as World Health Organization functional class IV. Two patients in the LT group had heritable PAH. Age was higher in the death group than in the LT group. There were no differences in sex, diagnosis, or treatment with i.v. epoprostenol, ERA, or PDE5i between the 3 groups. The periods from diagnosis to treatment, from diagnosis to registration, and from treatment to registration were similar between the 3 groups. The median period from diagnosis to epoprostenol treatment, however, was significantly shorter in the survival group (58 days; IQR, 29–109 days) than in the LT group (378 days; IQR, 91–1,079 days) and the death group (545 days; IQR, 115–1,451 days).

Table 2 compares hemodynamics at registration between the 3 groups. Mean PAP in the LT group was higher than that in the survival group. Other hemodynamic parameters did not differ between the 3 groups.

RHC After LT Registration

RHC was performed at LT registration and during the follow-up period in 8 patients in the survival group, in 13 in the LT group, and in 13 in the death group. The median interval between baseline and last follow-up hemodynamic studies was significantly longer in the survival group (15.3 years; IQR, 12.9–17.3 years) than in the LT group (3.3 years; IQR, 1.6–5.9 years) and the death group (4.3 years; IQR, 2.4–6.59 years; P<0.01). Change in treatment from

Table 1. Patient Characteristics at LT Registration vs. Outcome

	Survival (n=9)	LT (n=27)	Death (n=21)	P value
Sex (M/F)	2/7	9/18	7/14	0.72
Age (years)	30±9	20±11	31±12*	<0.01
Diagnosis				
Idiopathic/heritable PAH	7 (77)	24 (89)	19 (90)	0.60
PAH associated with CHD	2 (23)	3 (11)	2 (10)	0.60
Treatment with PAH-specific drugs				
I.v. epoprostenol	8 (89)	21 (78)	18 (86)	0.66
ERA	3 (33)	6 (22)	12 (57)	0.08
PDE5i	3 (33)	7 (26)	10 (48)	0.29
Duration (days)				
Diagnosis to treatment	29 (8–58)	274 (35–1,079)	275 (14–803)	0.13
Diagnosis to registration	286 (196–613)	1,146 (780–1,918)	1,141 (516–2,384)	0.19
Diagnosis to epoprostenol	58 (29–109)*	378 (91–1,079)	545 (115–1,451)	0.01
Treatment to registration	159 (140–559)	398 (178–1,137)	357 (193–1,037)	0.43
Time to registration				
Registration before 2005	6 (67)	6 (22)	10 (48)	0.48

Data given as mean±SD, n (%) or median (IQR). *P<0.05 vs. LT group. CHD, congenital heart disease; ERA, endothelin receptor antagonist; LT, lung transplantation; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitor.

Table 2. Hemodynamic Parameters at LT Registration vs. Outcome

	Survival	LT	Death	P-value
HR (beats/min)	79±12	89±13	83±17	0.16
SBP (mmHg)	99±15	102±14	105±20	0.76
PAP (mmHg)	55±7	67±14*	59±13	0.04
RAP (mmHg)	6±4	7±4	8±4	0.44
PAWP (mmHg)	7±3	9±5	9±4	0.34
CI (L/min/m^2)	2.7±0.8	2.5±0.7	2.7±1.5	0.76
PVR (Wood units)	13±5	17±6	15±7	0.25
BNP (pg/dL)	152 (67–473)	219 (76–334)	286 (85–477)	0.93
TRPG (mmHg)	96±21	95±21	91±22	0.82
6MWD (m)	322±95	350±57	320±102	0.72

Data given as mean±SD or median (IQR). *P<0.05 vs. waiting group. 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; CI, cardiac index; HR, heart rate; LT, lung transplantation; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SBP, systolic blood pressure; TRPG, tricuspid regurgitation pressure gradient.

Table 3. Change in PAH-Specific Drugs vs. Outcome

	Survival (n=8)		LT (n=13)		Death (n=13)	
	R	FU	R	FU	R	FU
No drugs	0	0	2	1	2	0
Monotherapy						
EPO	6	0	9	6	5	1
ERA	0	0	0	1	0	0
PDE5i	0	0	0	0	0	0
Double combination therapy						
EPO+ERA	0	0	1	0	0	1
EPO+PDE5i	0	0	0	1	0	0
ERA+PDE5i	0	0	1	0	1	0
Triple combination therapy						
EPO+ERA+PDE5i	2	8	0	4	5	11
Epoprostenol dose (ng/kg/min)	20 (15–34)	65 (57–114)	17 (14–29)	121 (111–160)	21 (20–44)	71 (44–122)

Data given as n or median (IQR). EPO, epoprostenol; ERA, endothelin receptor antagonist; FU, follow-up; R, registration for LT. Other abbreviations as in Table 1.

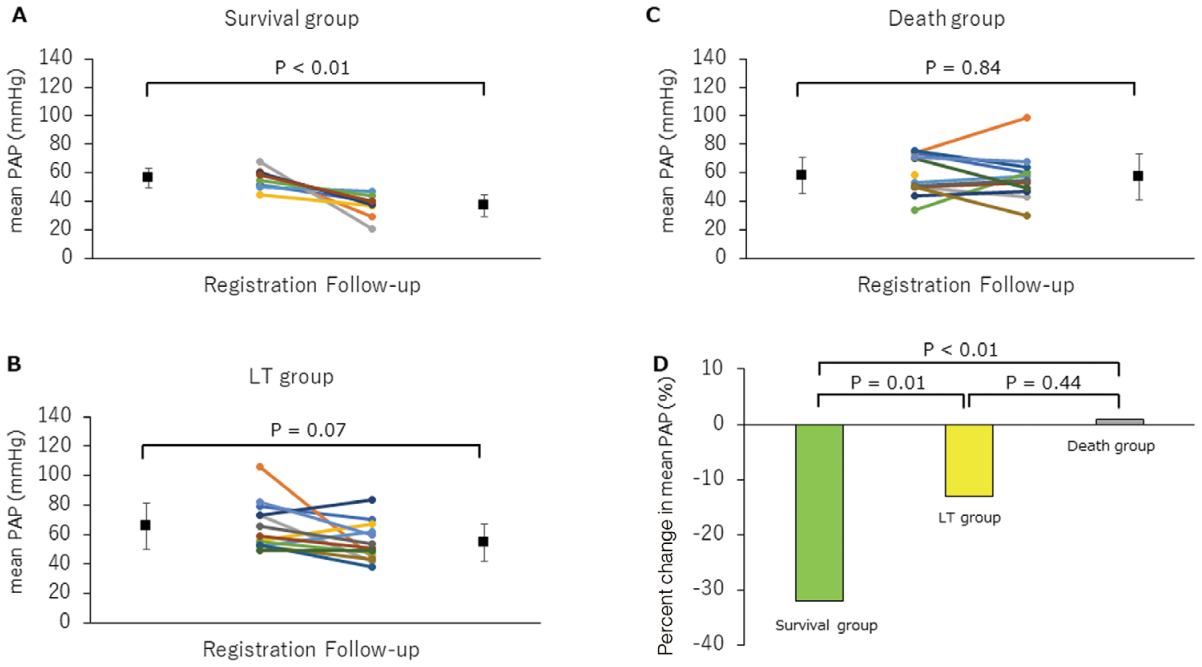

Figure 3. Change in mean pulmonary artery pressure (PAP) in the (**A**) survival group; (**B**) the lung transplantation (LT) group; and (**C**) the death group. (**D**) Percent change in mean PAP from baseline.

Table 4. Change in Hemodynamic Parameters vs. Outcome

	Survival (n=8)			LT (n=13)			Death (n=13)		
	R	FU	P-value	R	FU	P-value	R	FU	P-value
HR (beats/min)	77±11	77±9	0.86	89±10	88±13	0.40	76±15	88±15	0.03
SBP (mmHg)	98±16	98±10	0.44	101±14	103±7	0.48	111±23	100±13	0.03
RAP (mmHg)	4 (3–8)	5 (4–6)	0.92	6 (3–7)	8 (6–10)	0.18	6 (3–9)	8 (5–10)	0.24
PAWP (mmHg)	7±3	8±3	0.76	10±6	11±4	0.51	9±4	11±4	0.39
CI (L/min/m²)	2.5 (2.1–2.9)	2.6 (2.2–2.9)	0.73	2.4 (2.2–2.6)	2.8 (2.1–3.2)	0.12	2.2 (1.6–2.9)	3 (2.6–3.7)	0.04
PVR (Wood units)	12 (11–16)	10 (7–12)	0.61	16 (12–18)	8 (7–14)	0.02	16 (10–23)	11 (7–5)	0.08
BNP (pg/dL)	190 (94–576)	33 (18–68)	0.04	138 (66–309)	109 (41–247)	0.51	143 (40–429)	116 (27–145)	0.31
TRPG (mmHg)	99±21	63±24	0.15	91±12	85±24	0.95	90±27	94±31	0.52

Data given as mean±SD or median (IQR). Abbreviations as in Table 2.

registration to last follow-up is given in **Table 3**. All patients in the survival group were treated with triple combination therapy by addition of ERA and PDE5i after LT registration. Seven patients were treated with only i.v. epoprostenol, 1 patient was treated with double combination therapy and 4 patients were treated with triple combination therapy after LT registration in the LT group. Eleven patients were treated with triple combination therapy after LT registration in the death group. Average dose of epoprostenol was 20 ng/kg/min (15–34 ng/kg/min) in the survival group, 17 ng/kg/min (14–29 ng/kg/min) in the LT group and 21 ng/kg/min (20–44 ng/kg/min) in the death group at registration. Dose of epoprostenol increased in all groups at follow-up but there was no significant difference between the 3 groups (P=0.07). Maximum epoprostenol dose was 102 ng/kg/min (range, 77–136 ng/kg/min) in the survival group, 139 ng/kg/min (range, 114–172 ng/kg/min) in the LT group and 102 ng/kg/min (range, 60–180 ng/kg/min) in the death group. There was no significant difference in maximum epoprostenol dose between the 3 groups (P=0.55). Latest epoprostenol dose was 53 ng/kg/min (range, 34–84 ng/kg/min) in the survival group, 121 ng/kg/min (range, 111–155 ng/kg/min) in the LT group and 91 ng/kg/min (range, 50–131 ng/kg/min) in the death group. Latest dose of epoprostenol in survival group was lower than that in the LT and death groups (P=0.05).

Figure 3 shows changes in mean PAP from LT registration to follow-up examination. Mean PAP significantly decreased in the survival group (from 56±7 to 37±8 mmHg, P<0.01; **Figure 3A**) but not in the LT group (from 66±16 to 55±13 mmHg, P=0.07; **Figure 3B**) or the death group

Table 5. Risk Factors for Death After LT Registration

Variables	HR (95%CI)	P-value
Age at registration	1.02 (0.92–1.12)	0.72
Male	1.57 (0.44–5.61)	0.49
IPAH	1.93 (0.41–9.08)	0.40
Epoprostenol	0.51 (0.12–2.14)	0.36
Mean PAP at registration	0.97 (0.93–1.03)	0.34
CI at registration	1.53 (0.91–2.56)	0.10
BNP at registration	1.01 (0.99–1.00)	0.40
%reduction of mean PAP <15%	0.19 (0.04–0.92)	0.04

IPAH, idiopathic pulmonary arterial hypertension. Other abbreviations as in Table 2.

(from 58±13 to 57±16 mmHg, P=0.84; **Figure 3C**). The percent change in mean PAP after LT registration was significantly greater in the survival group (−32%) than in the LT group (−13%) or the death group (1%; P<0.01; **Figure 3D**). Other hemodynamic parameters are given in **Table 4**. Cardiac index significantly increased in the death group; pulmonary vascular resistance significantly decreased in the LT group. BNP significantly decreased in the survival group. There were no significant differences in other parameters between LT registration and follow-up examination in the 3 groups.

Predictors of Survival After LT Registration

On Cox proportional hazards analysis, percent reduction in mean PAP >15% after LT registration was an independent predictor of survival. Age, sex, idiopathic PAH, use of epoprostenol, mean PAP, cardiac index and BNP at registration were not significant independent predictors of survival (**Table 5**).

Discussion

Patients registered for LT generally have poor prognosis unless LT is performed. In the present study, however, some patients registered for LT had marked reduction in PAP and long-term survival without LT. These patients underwent i.v. infusion of epoprostenol soon after diagnosis of PAH. A percent reduction in mean PAP >15% from baseline was an independent predictor of survival.

The mortality rates in PAH patients on the LT waiting list range from 18% to 41%.[5–7] Between 1997 and 2013 in Japan, 199 patients underwent LT and 302 died while awaiting LT.[8] Dandel et al reported that 26 of 59 listed patients died while waiting for LT, despite a median waiting time of only 2.9 months.[6] There was no significant difference in PAP at the time of LT registration between patients who underwent LT and those who died before LT.[6] Hence, long-term survival in patients registered on the LT waiting list is generally not expected. In the present study, 9 patients (15%) had long-term survival after registration on the LT waiting list. In these patients, mean PAP markedly decreased from baseline. Generally, pulmonary hypertension seldom improves after patients are considered candidates for LT because these patients do not respond to medical therapy.

Why did some patients have a decrease in PAP after registration on the LT waiting list at the present center? LT was launched in Japan in 1999, but the number of donors has been very small, and the waiting period is longer than 3 years after registration. Therefore, many patients undergo living donor LT rather than cadaveric donor LT.[4] Patients without indications for living donor LT are treated with additional or augmented medical therapy. Our therapy of choice was high-dose i.v. epoprostenol infusion, because high-dose epoprostenol markedly decreases mean PAP in patients with idiopathic PAH.[9,10] Interestingly, patients in the survival group received i.v. epoprostenol sooner after diagnosis of PAH than patients in the other groups. Seven patients (78%) in the survival group were registered before the first follow-up RHC. Fifteen patients (56%) in the LT group were registered before the first follow-up RHC. Twelve patients (57%) in the death group were registered before the first follow-up RHC. Although these differences might lead to the shorter periods from diagnosis to epoprostenol use, early i.v. epoprostenol might explain the further decrease in mean PAP after registration on the LT waiting list. Another strategy for medical therapy is the addition of other PAH-specific drugs. In Japan, bosentan (an ERA) became available in 2005 and sildenafil (a PDE5i) became available in 2007. The addition of bosentan significantly decreases PAP in patients already receiving high-dose epoprostenol.[11] Early introduction of high-dose epoprostenol and the addition of ERA and PDE5i can decrease mean PAP, which contributes to long-term survival. The physician can change the LT list status from "listed" to "pending" in patients whose pulmonary hypertension improves after LT registration. This is known as the "inactive system" in Japan. Patients on inactive status remain on the waiting list but cannot receive LT if a donor becomes available. In 7 patients in the non-LT group who survived longer than the average waiting period, the status was changed to pending. Three patients in the non-LT group who had good response after LT registration were taken off the LT list. We kept the other patients on the list, according to their preference.

The percent change in mean PAP after registration was −32% in the survival group, which was greater than that in the LT group (−13%) and in the death group (1%). A percent reduction in mean PAP >15% was an independent predictor of long-term survival after registration. Is a strategy of lowering mean PAP an appropriate goal for the treatment of PAH? In a guideline used worldwide, lowering mean PAP is not named as a treatment goal for PAH patients.[2] Mean PAP <42.5 mmHg, however, is associated with good long-term survival in patients with idiopathic PAH.[12] Maximum lowering of mean PAP might be a meaningful goal for treatment of PAH. Multidimensional risk assessment or risk score provides a better estimation of short- or long-term prognosis than individual parameters.[13] Further investigation is required to determine whether lowering mean PAP is an effective strategy for long-term survival in patients with PAH. Although aggressive treatment with upfront triple combination therapy including i.v. epoprostenol may significantly improve prognosis,[14] physicians must refer the patients with end-stage PAH who are unresponsive to optimal medication to institutions for LT. Exercise capacity and right heart function is a stronger predictor of survival than hemodynamic parameters. We did not examine the cardiopulmonary exercise test at registration. Echocardiography was performed in all patients, but right heart function parameters such as TAPSE and RVFAC were not examined at registration. Right heart function was not evaluated on heart magnetic resonance imaging. These parameters should be examined at LT

registration because these parameters are predictors of survival.

The present patients seem very young. Bilateral LT is needed for patients with PAH. The criterion for bilateral LT in Japan is age <55 years. Idiopathic PAH accounted for 90% of the present cases, and the prevalence of idiopathic PAH is high at a young age. The present patients were therefore very young for these reasons. In this study, 18 patients received a living donor LT, which is a relatively high percentage. There were few cadaveric donors in Japan until 2010 because of the organ transplant law at the time. Data on living donor LT and cadaveric LT are given in **Supplementary Table 2**. Fourteen patients in the living donor LT group and 6 patients in the cadaveric LT group were registered for LT until 2010, at which time LT was carried out. Patient condition, attitude at the time of LT, family structure, family attitude and situation, and the attitude at the present center might have influenced the high percentage of living donor LT.

In the present study the interval from baseline to last follow-up was longer in the survival group than in the LT group and the deat group. There was no significant difference in median interval from baseline to first follow-up between the 3 groups (survival group, 0.6 years; IQR, 0.4–0.9 years; LT group, 0.8 years; IQR, 0.4–1.6 years; and death group, 0.9 years; IQR, 0.6–1.1 years; P=0.45). The latest guideline recommends regular follow-up assessment including catheterization to evaluate the severity or treatment response.[15] Regular follow-up including catheterization after LT registration are needed to evaluate severity or treatment response.

Study Limitations

This study had several limitations. This was a retrospective, single-center study and the patient population was small. To confirm the present results, a large-scale cohort study using a larger registry is required. Lung allocation score is used to prioritize list candidates in USA and a high-priority list is used to prioritize list candidates in France. In contrast, these systems have not yet been adopted in Japan. Instead, patients deteriorating on optimal medical therapy are registered for LT in Japan. Because the waiting list period is very long in Japan, we might judge the patients as unresponsive to optimal medical therapy too early. As a result, some patients might be referred to transplantation too early before the first examination after treatment introduction. We included patients with CHD in this study. Patients with CHD have particularities of long-term outcome and management, which might have affected the results. The percentage of patients in the hemodynamic subanalysis also differed between the 3 groups (89% in the survival group, 62% in the death group and 48% in the LT group), most likely due to patient adherence and to doctor routine management, as well as to the number of patients who died in the death group or who received LT in the LT group in the short term after registration. Despite the present limitations, the present study will help physicians to determine treatment strategies in patients with severe PAH.

Conclusions

Even after LT registration, patients who received epoprostenol infusion soon after diagnosis of PAH often had a marked reduction in PAP and long-term survival without LT.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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