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Pulmonary haemodynamics after single-lung transplantation for end-stage pulmonary parenchymal disease

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Pulmonary haemodynamics after single-lung transplantation for end-stage pulmonary parenchymal disease. Ø. Bjørtuft, S. Simonsen, O.R. Geiran, J.G. Fjeld, E. Skovlund, J. Boe. ©ERS Journals Ltd 1996.

ABSTRACT: In a prospective study, we investigated the effect of single-lung transplantation (SLT) on pulmonary haemodynamics and the relationship between pulmonary hypertension (PH) and the fraction of perfusion to the transplant in patients with end-stage pulmonary parenchymal disease.

Twenty four SLT recipients were included in the study, 19 with chronic obstructive pulmonary disease (COPD), two with sarcoidosis and three with fibrosing alveolitis. Spirometry, determination of arterial blood gas values, perfusion scintigraphy and right heart catheterization were performed before and 1, 6, 12 and 24 months after transplantation. Patients with a mean pulmonary artery pressure ($\bar{P}$pa) ≥20 mmHg before transplantation were defined as having PH (PH group, 15 patients) and the remainder (9 patients) constituted the non-PH group.

In the PH group, $\bar{P}$pa and pulmonary vascular resistance (PVR) were significantly decreased after transplantation: 28±2 to 18±1 mmHg and 288 to 161±11 dyne·s^{-1}·cm^{-5}, respectively (mean±SEM). In the non-PH group, the haemodynamic parameters were unchanged after transplantation. Over the 2 year follow-up period, no significant change was found in $\bar{P}$pa and PVR, nor any difference between the PH and non-PH group. There was no significant difference between the two groups in terms of pulmonary perfusion to the graft.

In conclusion, patients with pulmonary hypertension obtain pulmonary haemodynamics within the normal range after single-lung transplantation. Presence or absence of pulmonary hypertension before transplantation does not influence perfusion to the graft. These findings persist up to 2 yrs, despite the coexistence of an "end-stage" native lung and a lung transplant.

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In patients with end-stage pulmonary parenchymal disease, single-lung transplantation (SLT) is established as a treatment with acceptable survival [1], and satisfactory medium term pulmonary function [2, 3].

End-stage pulmonary parenchymal diseases are associated with increased pulmonary artery pressure (Ppa) in the majority of patients [4–6]. In these patients, SLT improves pulmonary haemodynamic abnormalities in the early postoperative period [7, 8], but scarce data are available during follow-up in patients with moderately increased Ppa [9]. On the other hand, in patients with primary pulmonary hypertension (PH) and other causes of severe PH, SLT has recently been associated with normalized pulmonary haemodynamics persisting for 4 yrs [10]. The impact of PH on survival and functional status in SLT is, however, controversial [8, 10].

After SLT for pulmonary parenchymal disease, the mean fraction of perfusion to the transplanted lung is 70–80%, but with individual values ranging 50–95% [2, 3, 11, 12]. The relationship between PH before transplantation and the fraction of perfusion to the allograft has not previously been studied.

We have, therefore, conducted a prospective study to evaluate the effect of SLT on pulmonary haemodynamics in patients with pulmonary parenchymal disease. The investigations were performed during a 2 year follow-up period after transplantation, and include the relationship between PH and the relative perfusion to the transplant.

Patients and methods

Between March 1990 and March 1994, 27 patients with end-stage pulmonary parenchymal disease underwent single-lung transplantation. The operative technique, immunosuppression and follow-up have been described previously [13, 14]. Three patients died early postoperatively. The diagnosis, functional characteristics before transplantation and causes of death are summarized in table 1. No follow-up assessments are available in these patients and, as a result, they have not been included in the study. The 24 survivors (mean age 50 yrs, range 40–60 yrs) with a mean observation time after transplantation of 30 months (range 13–61 months) are the basis of this report. Demographic data are shown in table 2.

Table 1. – Clinical characteristics of the three patients who died early postoperatively

TX No.	Diagnosis	Age yrs	$\bar{P}_{pa\dagger}$ mmHg	Cause of death	Time after TX weeks
4	Sarcoidosis	53	60	Pneumonia, ARDS	1
20	Chronic thromboembolic PH	33	48	CMV pneumonitis	6
24	FA	64	44	Coronary ischaemia	2

TX: treatment (transplantation); $\bar{P}_{pa\dagger}$: pre-operative mean pulmonary artery pressure; ARDS: adult respiratory distress syndrome; PH: pulmonary hypertension; CMV: cytomegalovirus; FA: fibrosing alveolitis.

Table 2. – Demographics of the 24 surviving single-lung transplanted patients

	Pts n
Sex	
Male/Female	13/11
Aetiology	
COPD	19
FA	3
Sarcoidosis	2
Transplantation	
Right/left lung	13/11

Pts: patients; COPD: chronic obstructive pulmonary disease; FA: fibrosing alveolitis.

The pretransplant assessment included spirometry, determination of arterial blood gas values, pulmonary perfusion scintigraphy and right heart catheterization. After transplantation, the same tests were repeated after 1, 6, 12 and 24 months. In the late follow-up period, six recipients died. The causes of death were: acute pancreatitis (patient No. 3, 58 months after transplantation); malignant melanoma (patient No. 8, 8 months); obliterative bronchiolitis (patient No. 9, 14 months); bronchial stenosis (patient No. 16, 9 months); obliterative bronchiolitis and intra-abdominal bleeding after liver biopsy (patient No. 19, 10 months); and massive haemoptysis (patient No. 26, 2 months). Three patients were retransplanted on the contralateral side because of bronchiolitis obliterans syndrome [15] 11, 19 and 39 months after the first transplantation, and were excluded from further follow-up. The number of patients at the different follow-up times are, thus, as follows: before and 1 month after transplantation, 24 patients; after 6 months, 19 patients; after 1 year, 18 patients; and after 2 yrs, 10 patients (7 patients had an observation time of between 12 and 24 months, leaving 10 with a 24 month follow-up).

Patients with a mean pulmonary artery pressure ($\bar{P}_{pa}$) of ≥20 mmHg before transplantation were defined as having pulmonary hypertension [16], constituting the PH group. Patients with a $\bar{P}_{pa}$ of <20 mmHg were defined as the non-PH group.

Right heart catheterization

After fasting overnight, a standard right heart catheterization was performed in the supine position without premedication. A 7F Cournand catheter was advanced from a femoral vein to the pulmonary artery. Pressures were measured with SensoNor 840 transducers (SensoNor, Horten, Norway) using a Mingograph 7 ink jet recorder (Siemens-Elema, Solna, Sweden) with zero reference level in the fourth intercostal space in the anterior axillary line. Cardiac output (CO) and oxygen uptake (V'_{O_2}) were measured using the Fick principle. The haemodynamic recordings were $\bar{P}_{pa}$ (mean, systolic and diastolic), pulmonary capillary mean wedge pressure (P_{pcw}), right atrial mean pressure (P_{ra}) and pulmonary vascular resistance (PVR). PVR was calculated as $(\bar{P}_{pa} - P_{pcw}) \cdot 80/CO$. Cardiac index (CI) is $CO \cdot m^{-2}$ body surface.

Pulmonary function tests

Dynamic lung volumes were measured using an automated pulmonary function unit (Gould 2400; Sensormedics, Bilthoven, The Netherlands). At least three satisfactory trials were performed. The highest forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded.

Arterial blood samples were obtained for measurements of arterial oxygen tension (P_{a,CO_2}) and arterial carbon dioxide tension (P_{a,CO_2}), with the patients resting and breathing room air.

Quantitative perfusion scintigraphy

Macroaggregated albumin (IFE MAA; Institutt for Energiteknikk, Norway) was labelled with ^{99m}Tc and an intravenous dose of 180 MBq in approximately 1 mL was administered during 1 min, with the patient in the supine position, breathing in and out slowly and deeply. With the camera in the dorsal position, the imaging was started immediately after the injection, and continued until a picture with 500,000 counts was obtained. Thereafter, using the same acquisition time as in the dorsal view, scintigrams from the anterior and from the four oblique views were taken. The perfusion of each lung was expressed as a percentage of the total counts in both lungs, using the arithmetic mean of the counts in the anterior and posterior view.

Statistical analysis

A mixed model analysis of variance (ANOVA) [17] with repeated measurements was used to analyse the data. In the tables, the results are presented as estimated mean ±SEM in each group before transplantation and after

Table 3. – Individual mean pulmonary artery pressure ($\bar{P}_{pa}$) values before and after transplantation

TX No.	Diagnosis	$\bar{P}_{pa}$ mmHg				
		Before	1 mo	6 mo	12 mo	24 mo
Patients with normal $\bar{P}_{pa}$ before transplantation						
8	COPD	16	18	-	Death 11 mo	
10	COPD	14	13	18	14	15
12	COPD	17	10	10	12	8
15	COPD	18	22	22	28	
16	FA	16	16	15	Death	
18	COPD	16	14	10	13	
21	FA	11	18	16	20	
23	COPD	17	16	10	25	
26	COPD	19	14	Death		
Patients with PH before transplantation						
1	Sarcoidosis	36	26	22	33	24
2	COPD	22	13	13	-	16
3	COPD	24	9	12	13	16
5	COPD	22	-	17	18	20
6	COPD	45	-	30	25	19
7	Sarcoidosis	36	28	-	Re-TX 11 mo	
9	COPD	29	14	17	-	Death 14 mo
11	COPD	29	16	18	22	19
13	COPD	20	14	19	17	14
14	COPD	24	12	16	17	16
17	COPD	30	21	24	18	Re-TX
19	COPD	25	12	20	Death	
22	FA	28	14	21	18	
25	COPD	22	16	14	18	
27	COPD	30	21	21	16	

TX: treatment (transplantation); -: missing value; Re-TX: retransplanted; COPD: chronic obstructive pulmonary disease; FA: fibrosing alveolitis; PH: pulmonary hypertension.

transplantation (corrected for time). A two-sample t-test was used to compare the values before transplantation between the PH and non-PH group. A p-value for the difference between groups is given. All the tests are two-sided, and a p-value of less than 0.05 is regarded as statistically significant.

Results

Fifteen patients (12 with chronic obstructive pulmonary disease (COPD), two with sarcoidosis, and one with fibrosing alveolitis (FA)) had PH before transplantation and constituted the PH group, while nine patients (seven with COPD and two with FA) made up the non-PH group (table 3). All of the individual $\bar{P}_{pa}$ values in the observation period are presented in table 3. Ten patients were followed for 2 yrs, and at 24 months they had a $\bar{P}_{pa}$ of 17±1 mmHg.

Pulmonary haemodynamics in the PH and non-PH group before and after transplantation at 1, 6 and 12 months are presented in table 4.

$\bar{P}_{pa}$ and PVR were significantly greater in the PH group compared to non-PH group before transplantation (table 5). The P_{a,O_2} was lower in the PH group ($p<0.05$), while FVC, FEV1, and P_{a,CO_2} were not significantly different between the two groups (table 5).

After transplantation $\bar{P}_{pa}$ and PVR were significantly decreased in the PH group (table 5).

Using the mixed model ANOVA and including all

Table 4. – Pulmonary haemodynamics in patients with pulmonary hypertension (PH) and without (non-PH), before and after transplantation

	Before	1 month	6 months	12 months
Non-PH group				
Pts n	9	9	7	6
$\bar{P}_{ra}$ mmHg	1±1	0±1	1±1	2±0
$P_{pa,syst}$ mmHg	24±1	27±2	24±3	32±5
$P_{pa,diast}$ mmHg	10±1	9±1	8±1	11±2
$\bar{P}_{pa}$ mmHg	16±1	16±1	14±2	19±3
$\bar{P}_{pcw}$ mmHg	6±1	7±1	6±1	10±1
PVR dynes·s^{-1}·cm^{-5}	177±28	105±10	145±22	136±27
CI L·min^{-1}·m^{-2}	2.7±0.2	3.4±0.3	3.0±0.2	3.1±0.33
V'_{O_2} mL·min^{-1}	228±16	237±13	244±15	232±18
PH group				
Pts n	15	15	14	12
$\bar{P}_{ra}$ mmHg	5±1	1±1	3±1	3±1
$P_{pa,syst}$ mmHg	40±3	27±2	30±2	30±1
$P_{pa,diast}$ mmHg	18±2	11±1	11±1	11±1
$\bar{P}_{pa}$ mmHg	28±2	17±2	19±1	20±1
$\bar{P}_{pcw}$ mmHg	10±2	6±1	10±1	9±1
PVR dynes·s^{-1}·cm^{-5}	288±30	149±11	142±17	163±19
CI L·min^{-1}·m^{-2}	3.1±0.2	3.4±0.2	3.2±0.2	3.0±0.2
V'_{O_2} mL·min^{-1}	222±12	208±11	215±9	201±7

Values are presented as mean±SEM. Pts: patients; $\bar{P}_{ra}$: mean right atrial pressure; P_{pa}: pulmonary artery pressure; syst: systolic; diast: diastolic; $\bar{P}_{pa}$: mean pulmonary artery pressure; $\bar{P}_{pcw}$: mean pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; CI: cardiac index; V'_{O_2}: oxygen uptake.

Table 5. – Arterial blood gas values, lung volumes, pulmonary vascular resistance, mean pulmonary artery pressure and perfusion to the transplanted side in patients with pulmonary hypertension (PH) and without (non-PH) before and after transplantation (estimated mean at 1, 6, 12 and 24 months)

	Before transplantation		After transplantation	
	Non-PH	PH	Non-PH	PH
P_{a,O_2} kPa	7.8±0.5	6.8±0.2*	10.6±0.6	9.9±0.4
P_{a,CO_2} kPa	6.1±0.5	7.1±0.6	5.0±0.2	5.4±0.2
FVC L	2.18±0.40	1.64±0.18	2.84±0.24	2.32±0.40
FEV1 L	0.82±0.15	0.71±0.17	1.52±0.14	1.40±0.11
PVR dynes·s^{-1}·cm^{-5}	177±26	288±32*	130±14	161±11^{+}
$\bar{P}_{pa}$ mmHg	16±1	28±2**	16±1	18±1^{+}
Perfusion %	48±5	48±2	69±3	76±2

Values are presented as mean±SEM in each group before transplantation, estimated mean values±SEM (measurements at 1, 6, 12 and 24 months) after transplantation (mixed model ANOVA with repeated measurements) and the p-values for comparison between the two groups. P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; $\bar{P}_{pa}$: mean pulmonary artery pressure; PVR: pulmonary vascular resistance. Perfusion: perfusion to side of transplantation as a percentage of total perfusion; ANOVA: analysis of variance. *,**: p<0.05, <0.01 *vs* non-PH; $^{+}$: p<0.05 *vs* before transplantation.

the observations (1, 6, 12 and 24 months after transplantation), the pulmonary function, $\bar{P}_{pa}$, PVR and the perfusion to transplanted side in the two groups were analysed (table 5). There was no significant difference between the PH group and the non-PH group in any of these parameters, and there was no change during the observation period after the transplantation.

Figure 1 shows that half of the total perfusion before transplantation was directed to the lung that was replaced by the allograft. After transplantation, the percentage of total perfusion to the graft increased to approximately 70% both in the PH and non-PH group. The correlation between $\bar{P}_{pa}$ (dependent variable) and P_{a,O_2} and FEV1 was also analysed using the mixed model ANOVA with the inclusion of a covariate (P_{a,O_2} or FEV1). A significant correlation was found between $\bar{P}_{pa}$ and P_{a,O_2} (p<0.001), with an estimated change in $\bar{P}_{pa}$ = -1.69 mmHg with a 1 kPa increase in P_{a,O_2}. There was no correlation between $\bar{P}_{pa}$ and FEV1 (p=0.91).

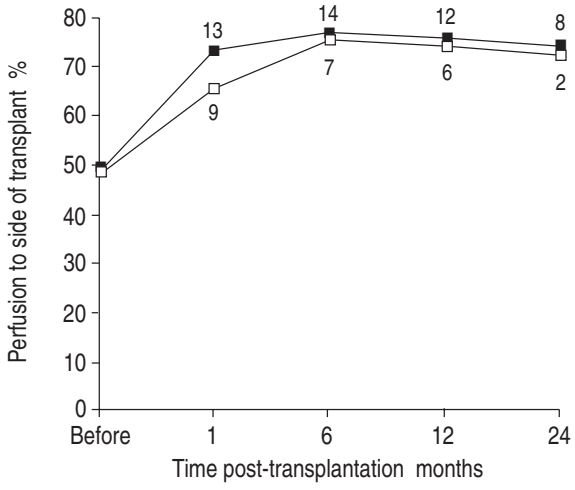

Fig. 1. – Percentage of total perfusion to the side of the transplant before and at different time intervals after transplantation. —■— : PH group, *i.e.* patients with a mean pulmonary artery pressure ≥20 mmHg before transplantation; —❑— : non-PH group, *i.e.* patients with mean pulmonary artery pressure <20 mmHg before transplantation. The number of patients in the two groups is indicated at the value points. PH: pulmonary hypertension.

There was no correlation between perfusion to the transplanted side (dependent variable) and $\bar{P}_{pa}$ and PVR (p=0.172 and p=0.86, respectively).

Discussion

In the present study, the patients with PH had mild-to-moderately increased $\bar{P}_{pa}$ values prior to transplant. Their pulmonary haemodynamics were within the normal range after SLT, and remained so after 2 yrs. The patient group with normal $\bar{P}_{pa}$ before transplantation had unchanged haemodynamics after transplantation. Furthermore, the percentage of pulmonary perfusion to the transplanted side was not significantly different in the two groups.

There are no previous reports of serial measurements of pulmonary haemodynamics after SLT for pulmonary parenchymal disease. In one report, however, with a single follow-up measurement in five patients with pulmonary fibrosis and PH (mean observation time 18 months, range 2–29 months), the $\bar{P}_{pa}$ was 18 mmHg [9], *i.e.* similar to the present results. In severe PH because of pulmonary vascular disease, SLT has become a feasible therapeutic option with normalized pulmonary haemodynamics and satisfactory functional improvement during follow-up [10, 18, 19]. These results persisted up to 4 yrs [10], and the haemodynamic results were similar to those in the present study. After 2 yrs (11 patients) and 4 yrs (6 patients) $\bar{P}_{pa}$ was 21 mmHg, compared to a $\bar{P}_{pa}$ of 17 mmHg after 2 yrs (10 patients) in the present study. A normal $\bar{P}_{pa}$ persisting for 2–4 yrs after transplantation despite PH before transplantation indicates that a successful SLT is accompanied by normalized pulmonary haemodynamics in the long-term follow-up.

After SLT for severe pulmonary hypertension, there was a mismatch between ventilation and perfusion distributed to the transplant, approximately 50 and 80%, respectively. Even with this mismatch, the functional status was satisfactory [10]. In the non-PH group in the present study, the lungs had only a slightly elevated PVR before transplantation and, theoretically, the opposite mismatch might appear; perfusion might be distributed evenly between the native and transplanted

lungs, while ventilation would be directed mainly to the transplanted lung. However, the present study revealed a similar percentage of perfusion to the graft as in previous reports and, in addition, demonstrated that the perfusion to the transplanted lung was not significantly different between patients with and without PH before transplantation. Furthermore, this pattern persisted for at least 2 yrs.

Pulmonary artery pressure in pulmonary parenchymal disease has previously been shown to be inversely correlated with P_{a,O_2} [16, 20–22]. The correlation between FEV1 and $\bar{P}_{pa}$ is controversial; in one study, no correlation was found [23], whilst another long-term study reported a weak inverse correlation [16]. In the present study, in accordance with these results, a significant inverse correlation was found between P_{a,O_2} and $\bar{P}_{pa}$, but no correlation between FEV1 and $\bar{P}_{pa}$.

SLT is the most effective way of utilizing available donor organs. However, in one study a $\bar{P}_{pa}$ greater than 30 mmHg before transplantation was reported to be associated with lower 1 year survival, prolonged intensive care unit stay and less symptomatic improvement. Accordingly, the authors raised the question of whether SLT may be suboptimal therapy in patients with PH [8]. In another study of SLT for severe PH, the survival and functional results were good, but the PH patients were not compared with non-PH patients [10]. The three patients in the present study with early postoperative death had a $\bar{P}_{pa}$ greater than 30 mmHg, but their causes of death are difficult to associate with PH. The other six deaths had a $\bar{P}_{pa}$ below 30 mmHg, and three were in the PH and three the non-PH group. Some controversy, therefore, still exists about the impact of PH on the outcome of SLT. Further long-term studies of the effects of PH in SLT appear to be warranted.

In conclusion, the occurrence of mild-to-moderate pulmonary hypertension before transplantation is not associated with elevated pressures in the pulmonary circulation after transplantation and does not influence perfusion to the graft. The present findings indicate that the coexistence of a lung graft with normal function and an end-stage diseased native lung has no negative impact on the pulmonary haemodynamics in long-term follow-up.

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