Twinned single-lung transplantation: a privileged model for the study of recipient-dependent factors of outcome†

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Abstract

OBJECTIVES: Lung transplantation is the only life-saving treatment for end-stage respiratory disease. The outcome will depend on the graft quality, surgical conditions and recipient factors. Twinned single-lung transplantation defines as two different recipients treated with lung grafts from the same donor. Recipient-dependent factors of the outcome can be studied more accurately as the graft quality is supposed equal for both recipients.

METHODS: We reviewed all single-lung transplantations performed in France between 1998 and 2008 in the French registry run by the ‘Agence de Biomédecine’. Criteria for donor lung quality and twinned recipient data were recorded in a database. The whole medical history and the transplantation outcome were reviewed for each patient and compared with its twin recipient. We compared twins on the basis of their opposed characteristics and on the basis of the opposed endpoint outcome. Endpoints were primary graft dysfunction (PGD) grade III, and mortality at 1, 3 and 12 months.

RESULTS: A total of 387 single-lung transplantations were performed in 10 French centres; 180 were twinned recipients from 90 donors. Statistical analysis revealed a significantly different outcome for PGD only. PGD was significantly higher (P < 0.05) in fibrosis recipients compared with emphysema twins. In 28 pairs (31%), the outcome was discordant for PGD, and fibrosis was significantly more often involved compared with emphysema (P = 0.04). Sixty-two pairs had a similar outcome: two pairs showed PGD in both recipients while 60 pairs were free of PGD.

CONCLUSIONS: We conclude that recipient’s disease is a major determinant of the outcome. Fibrosis is associated with an increased risk for PGD.

Keywords: Lung transplantation • Fibrosis • Emphysema • Primary graft failure

INTRODUCTION

Lung transplantation is the only life-saving treatment for patients with end-stage respiratory disease. The outcome will be dependent on the graft quality, surgical conditions during graft retrieval and transplantation and recipient-dependent factors [1, 2]. Single-lung transplantation has the theoretical advantage compared with bilateral transplantation to increase the number of available organs by treating two different recipients from one donor. But, overall, survival after single-lung transplantation is significantly lower than that after bilateral transplantation [2, 3].

This difference may be first explained by dissimilar disease patterns between patients undergoing either single or bilateral transplantation. Bilateral transplantation will be performed for all respiratory diseases including younger patients affected with cystic fibrosis. Single-lung transplantation will be performed for non-suppurative respiratory diseases, fibrosis and obstructive diseases and in patients with comorbidity or older age. Besides, the outcome of the underlying lung disease conditions, which is known to be best in cystic fibrosis patients and worst in idiopathic pulmonary fibrosis [2] (Agence de la Biomédecine. Le rapport annuel de l’Agence de la Biomédecine 2009, bilan des activités de prélèvement et de greffe en France. http://www.agence-biomedecine.fr/annexes/bilan2009/accueil.php). On the other hand, the single-lung transplantation procedure is often considered as a satisfactory solution for patients considered too fragile to undergo a bilateral procedure.

To study more accurately the influence of recipient factors on the results of transplantation, we need a model, which is independent from donor characteristics and from surgical conditions.
Twinned single-lung transplantation meets these requirements: as two recipients are transplanted with lungs retrieved from the same donor, lung graft quality can be supposed equal for both recipients, and hence the outcome may be compared in accordance with recipient’s characteristics.

Only a few studies have focused on twinned single-lung transplantation. According to the theoretical advantage of improved organ sharing, some single-centre studies addressed the technical feasibility of twinning with the aim to increase the number of transplantation [3, 4]. For Glanville et al. the only consequence of twinned lung transplantation in the same centre was longer ischaemic time for the second transplanted recipient, but no consequence on early graft function could be obviated. Sommers et al. [5] studied the influence of the donor’s characteristics on the early post-transplantation period in 27 pairs.

Snell et al. [6] speculated that anatomical differences between right and left transplantation would determine the surgical conditions and compared the outcome of single-lung transplantation in 38 pairs. Twinned recipients had to receive the same immunosuppressive treatment, ischaemic time and preservation mode of the grafts had to be similar. These conditions were easily respected and supposed unvaried in a single-centre study. No difference was found between right and left single-lung transplantation. But, no correlation between twinned recipients was found regarding the occurrence of acute rejection or the degree of chronic rejection either: recipients transplanted from the same donor would have their own characteristics to explain for rejection complications. In the model of twinned single-lung transplantations, when all other conditions were controlled (immunosuppression, ischaemia and preservation mode of the graft), the difference in the outcome could only be explained by the influence of recipient-dependent factors. This study concluded that donor-dependent factors were not the major factor influencing the occurrence of acute or chronic rejection [6].

The Eurotransplant study was conducted on 45 pairs and has been so far the largest study conducted on twinned recipients [7]. Even if multicentric, this prospective study controlled all factors around transplantation by the common organization provided by the Eurotransplant system. The study concluded to a worse outcome for patients transplanted on the left side and for patients whose graft was harvested by a different team than the transplantation team. The authors recognized a possible bias by different immunosuppressive treatments and follow-up strategies from one centre to another [7].

Twinned single-lung transplantation enables to study the influence of recipient-dependent factors on the outcome of lung transplantation [6, 7]. However, donor and graft quality as well as surgery conditions, immunosuppressive treatments and follow-up strategies need to be controlled and provide overall comparable conditions for all studied recipients [7]. So far, only two studies on twinned pairs could aim at recipient-dependent factors. The aim of our study was to enlarge the number of studied twins and analyse the influence of their characteristics on the outcome of lung transplantation.

**MATERIALS AND METHODS**

**Patients groups**

We conducted a retrospective French national study. Among the 12 French centres performing lung transplantation, 10 agreed to share patient data. The French ‘Agence de Biomédecine’, which rules the organ sharing in France, listed from the French national registry all the patients having undergone single-lung transplantation in those centres between 1 January 1998 and 31 December 2008. Exhaustive data of their donors were extracted from the same registry, and all twinned recipients were identified.

As a next step, we reviewed all individual patient files in each of participating centre. Collected data concerned medical history before transplantation, lung retrieval and preservation, lung transplantation and consecutive medical follow-up. With exception of one centre, all data were recorded by a single observer.

**Indications for transplantation**

We pooled together all recipients transplanted for α1-emphysema, tobacco-related obstructive diseases and emphysema in one group entitled ‘emphysema’. We grouped all recipients with proven interstitial lung disease under the heading ‘fibrosis’, in case, an obstructive disorder was associated histologically proven interstitial fibrosis, we considered fibrosis as main diagnosis. Patients diagnosed with histiocytosis X were pooled with fibrosis as well.

The series included patients subjected to lung re-transplantation. When re-transplantation was performed on the opposite side to the first lung transplantation, we coded for the original diagnosis and a medical history of solid organ transplantation. When re-transplantation was performed on the same side or following bilateral lung transplantation, we coded for bronchiolitis obliterans syndrome (BOS) and the medical history of solid organ transplantation. Other recorded indications were cystic fibrosis and lymphangioleiomyomatosis.

**Graft quality**

For each single-lung recipient, we recorded the following donor characteristics: age, ABO blood group, chest radiograph, arterial partial oxygen tension (PaO2) under 100% inspired oxygen fraction (FiO2) and 5 cmH2O positive end-expiratory pressure (PEEP), smoking history, any chest trauma, aspect of tracheal aspiration, history of cardio-thoracic surgery, bacterial examination of the bronchial secretions and results of bronchoscopy.

**Lung retrieval and preservation**

For all grafts, the retrieval team was identified. We recorded the preservation solution for all grafts and the total ischaemic time defined by the time of aortic clamping in the donor and pulmonary artery de-clamping in the recipient. We could not get access to the time of arrival of the graft in the operating room for transplantation, and warm ischaemia is not known.

**Surgery**

We recorded the side of transplantation and some anecdotal cases of bilateral transplantation performed with a split left lung graft. The context and need for cardiopulmonary bypass (CPB) was also taken into account.
Recipient-dependent factors

For each recipient, we recorded the conditions of transplantation, follow-up and immunosuppressive treatment. We especially detailed the indication for transplantation with prior exposition to tobacco or to other inhaled lung pathogens (silica, asbestos, chemicals), medication related to the respiratory disease such as inhaled or enteral steroids and immunosuppressive treatment, the type of ventilation at the time of transplantation (passive oxygen, non-invasive ventilation or mechanical ventilation) and whether transplantation applied to the super-emergency status. Body mass index was calculated to monitor nutritional consequences of disease; pulmonary artery pressure (PAP) was monitored, and hypertension was defined as a mean pressure >35 mmHg. Right ventricle ejection fraction (RVEF) was assessed in all patients before transplantation by means of echocardiography or right isotopic ventriculography. Normal RVEF was set at 46 ± 7% [8, 9] and right ventricle insufficiency was recorded if RVEF was less than 40%.

We also listed factors related to an immune disorder or sensitization before transplantation: autoimmune factors (proven autoimmune systemic disease or the presence of somatic autoimmune antibodies prior to transplantation), recipients undergoing re-transplantation or with medical history of solid organ transplantation, prior blood transfusion, detectable anti-human leukocytes antigen (HLA) antibodies prior to surgery and medical history of pregnancy. Anti-HLA antibodies were detected in recipients before transplantation either by means of a complement-dependent cytotoxicity test or by means of a Luminex™ test after 2003.

Eventually, we checked for the history of alcohol abuse or drug addiction, medical history of oesophageal reflux and medical history of cancer. The donor/recipient mismatch on the blood group, gender and cytomegalovirus (CMV) was recorded as well.

Endpoints

We reviewed the immediate post-operative outcome to evaluate the occurrence of primary graft dysfunction (PGD) grade III as defined by the International Society for Heart Lung Transplantation (PaO₂/FiO₂ <200 and radiographic infiltrates consistent with pulmonary oedema) [10]. The medical follow-up of each recipient was reviewed to assess the occurrence of acute rejection episode or the diagnosis of chronic rejection or BOS; these events were dated and any change of the immunosuppressive regimen was recorded. Chronic rejection, BOS or chronic allograft dysfunction was recorded with their date of occurrence each time diagnosis was made by the chest physician in charge of the patient. If graft function was found stable during whole follow-up, we made sure with all relevant information available in the medical file and with the chest physician that there were no signs of graft rejection at the last follow-up session.

All recipient medical files were reviewed between May and July 2010; there was a minimum follow-up of 1 year for each surviving patient. Date of death was recorded for mortality and survival rate calculations. In surviving patients, the estimation of survival was calculated with a reference date set to 30 April 2010. If necessary, we made sure with the chest physician or with the general practitioner that the patient was still alive. No patients were found lost to follow-up.

Statistical analysis

All statistical analysis was performed with SPSS17 software (SPSS Inc., Chicago, IL, USA). We supposed normality of the studied population. Categorical values were compared using a χ² test. Quantitative and continuous values were compared using an unpaired t-test except for graft ischaemia time. Two different ischaemia times were considered imposed to the same graft (right and left lung from the same donor) and a paired t-test was used. The Kaplan-Meier survival curves were constructed and compared using a log-rank test. Multivariate analysis was performed using a logistic regression. All results are expressed as the mean ± SEM or as median and range; P-value of ≤0.05 was considered significant.

RESULTS

General data

A total of 387 single-lung transplantations were performed by the 10 participating centres between 1998 and 2008. Among them, 90 donors were harvested to treat 180 twinned lung recipients.

Donors

All donors were heart-beating donors. The mean age of donors was 40 ± 14 years; 30 (33%) donors were females and 60 (67%) were men. The leading cause of brain death was stroke. Mean PaO₂ (FiO₂ 100% and PEEP 5 cmH₂O) was measured at 443 ± 90 mmHg. Immunization towards CMV was present in 36 (40%) donors.

Thirteen donors are considered as extended: four were aged over 65, one had PaO₂ at 119 mmHg, five experienced aspiration, two had a pleural effusion and one had a significant lung contusion (Table 1).

Lung preservation and transplantation

Mean ischaemic time measured was 265 ± 73 min. Fifteen (8%) recipients had graft ischaemic time over 360 min with a maximum measured at 540 min. Most of the grafts were harvested and preserved using Celsior™ solution (n = 64; 71%) followed by Perfadex® (n = 11; 12%). In nine donors (10%), the preservation solution could not be identified (Table 1).

Medical decision regarding immunosuppressive induction therapy was identified for 108 (60%). In 64 (36%) of 180 recipients, decision was made to give no induction therapy.

Following lung transplantation, all patients received an immunosuppressive therapy in accordance with the validated standards, with their clinical state or with particular medical conditions assessed before transplantation. In 138 (77%) recipients, immunosuppressive regimen consisted in a three-drug association of steroids to an antimetabolite and an anticalcineurin drug. In four patients, complete immunosuppressive therapy was not achieved either because of early death of the recipient or because of acute renal failure prohibiting use of anticalcineurin. In 38 (21%) patients, we could not identify
with precision the initial drug association, but we know that immunosuppressive therapy was given with respect to lung transplantation.

**Transplantation surgery**

All recorded procedures were performed in trained centres and consisted in single-lung transplantation. In three (1.7%) recipients from the same centre, a left lung graft was divided to perform lobar bilateral transplantation.

In 29 (16%) recipients, CPB was used during surgery. Only one recipient was put on extra-corporeal membrane oxygenation (ECMO) before surgery. ECMO was needed for eight (4.4%) patients in immediate post-operative course.

**Recipients**

Hundred and eighty recipients underwent twinned single-lung transplantation between 1998 and 2008. As defined by twinned single-lung transplantation, the number of right and left transplantation performed was the same. The mean age of recipients at the time of transplantation was 53 ± 10 years. Among them, we noticed 118 (66%) men and 62 (34%) women.

**Indications (Table 2)**

We found 83 (46%) patients transplanted for fibrosis, 71 (39%) recipients for emphysema and 10 (6%) recipients for re-transplantation. One patient was re-transplanted for the fourth time. We recorded two patients with cystic fibrosis; these patients underwent single-lung transplantation associated with the pneumonec- tomy of the opposite native lung.

**Other medical history**

We found 89 (49%) recipients with history of smoking. Overall, 103 (57%) recipients had prior exposure to a lung

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**Table 1: Donors and graft characteristics**

<table>
<thead>
<tr>
<th>Donors (n = 90)</th>
<th>General characteristics</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean 40 ± 14 years</td>
<td>Four donors &gt;65 years</td>
</tr>
<tr>
<td>Cause of brain death</td>
<td>Stroke 47% (n = 42)</td>
<td>Non-identified 1% (n = 1)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Meas 49 ± 44 h</td>
<td>32% (n = 29 donors)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Mean 443 ± 90 mmHg</td>
<td>31% (n = 28), &gt;48 h</td>
</tr>
<tr>
<td>PaO₂, FiO₂ 100% PEEP 5 cmH₂O</td>
<td>1% (n = 1), &lt;300 mmHg</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion prior to retrieval</td>
<td>26% (n = 23 donors)</td>
<td></td>
</tr>
<tr>
<td>Chest radiograph abnormality</td>
<td>6% (n = 5) gastric inhalation</td>
<td></td>
</tr>
<tr>
<td>Preservation solution</td>
<td>2% (n = 2) pleural effusion</td>
<td></td>
</tr>
<tr>
<td>Ischaemia time</td>
<td>27% (n = 1) lung trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean 265 ± 73 min</td>
<td>11% (n = 10) not identified</td>
</tr>
</tbody>
</table>

**Table 2: Global characteristics of recipients and transplantation outcome (recipients n = 180 and left lung transplantation = right lung transplantation = 90)**

<table>
<thead>
<tr>
<th>Indications</th>
<th>39% (n = 71) emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46% (n = 83) fibrosis</td>
</tr>
<tr>
<td></td>
<td>Others: 7% (n = 12) lymphangioleiomyomatosis; 6% (n = 10) retransplantation/BOS; 2% others: n = 2 cystic fibrosis, n = 1 bronchioloalveolar carcinoma, n = 1 destructed lung with cardiopulmonary congenital abnormality</td>
</tr>
<tr>
<td>Mean age</td>
<td>53 ± 10 years</td>
</tr>
<tr>
<td>Lung pathogen exposition</td>
<td>49% (n = 89) tobacco</td>
</tr>
<tr>
<td>Ventilation</td>
<td>13% (n = 24) silica, asbestos or X radiation</td>
</tr>
<tr>
<td>Medication</td>
<td>93% (n = 168) passive O₂ therapy</td>
</tr>
<tr>
<td>Immune state</td>
<td>26% (n = 46) non-invasive ventilation</td>
</tr>
<tr>
<td>Nutritional state</td>
<td>2% (n = 3) mechanical ventilation</td>
</tr>
<tr>
<td>Immune state</td>
<td>61% (n = 109) general steroids</td>
</tr>
<tr>
<td>Immune state</td>
<td>49% (n = 88) inhaled steroids</td>
</tr>
<tr>
<td>Immune state</td>
<td>25% (n = 45) immunosuppressive drugs</td>
</tr>
<tr>
<td>Immune state</td>
<td>12% (n = 21) &lt;18 kg/m²</td>
</tr>
<tr>
<td>Immune state</td>
<td>18% (n = 32) auto-immune somatic disorder</td>
</tr>
<tr>
<td>Immune state</td>
<td>(dismime)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>27% (n = 48) sensitized patients</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4% (n = 7) anti-HLA immunized patients</td>
</tr>
<tr>
<td>Need for CPB</td>
<td>17% (n = 30) right ventricle insufficiency</td>
</tr>
<tr>
<td>PGD grade III</td>
<td>22% (n = 39) PAP &gt; 35 mmHg</td>
</tr>
<tr>
<td>Survival</td>
<td>16% (n = 29) CPB during surgery</td>
</tr>
<tr>
<td>Mortality</td>
<td>20% (n = 36)</td>
</tr>
<tr>
<td>Survival</td>
<td>Mean 67 ± 5 months; 66% 1-year survival</td>
</tr>
<tr>
<td>Mortality</td>
<td>13% (n = 24) deceased 1 month</td>
</tr>
<tr>
<td>Mortality</td>
<td>20% (n = 37) deceased 3 months</td>
</tr>
<tr>
<td>Mortality</td>
<td>34% (n = 62) deceased 1 year</td>
</tr>
<tr>
<td>Other events</td>
<td>52% (n = 94) recipients one or more acute rejection</td>
</tr>
<tr>
<td>Other events</td>
<td>30% (n = 54) recipients chronic rejection</td>
</tr>
</tbody>
</table>
pathogen. In former smoker patients, emphysema patients were significantly more frequent \((P < 0.0001)\). In recipients with no smoking history, fibrosis patients were significantly more frequent \((P = 0.002)\). At transplantation time point, 46 (26%) patients had non-invasive ventilation and 3 (1.7%) had mechanical ventilation. In 13 (7%) patients, respiratory insufficiency reached a level needing transplantation on the emergency list.

Thirty (17%) patients had clinical and echocardiographic right ventricle insufficiency and 39 (22%) had mean PAP \(\geq 35\) mmHg measured either by echocardiography or by right heart catheterism.

We found 32 (18%) recipients with the disimmune disorder either related to autoimmune lung disease or related to a serum-positive autoimmune antibody. Besides, overall 48 (27%) recipients had a medical history of a prior sensitizing event either red blood cells transfusion, solid organ transplantation, bone marrow grafting or pregnancy. From those patients exposed to sensitization, only seven (4%) patients confirmed with biological proved anti-HLA antibody immunization. This rate is probably underestimated as the Luminex® test was not available for all patients during our study.

Prior to transplantation, we also found 9 (5%) patients with history of diabetes mellitus, 17 (9.4%) patients with hiatal hernia or reflux and 6 (3.3%) patients with weaned alcoholism.

Transplantation outcome

After transplantation, the mean mechanical ventilation duration was 123 ± 256 h. The mean duration stay in ICU and in hospital was 19 ± 22 and 50 ± 32 days, respectively.

During the transplantation procedure, the need for CPB occurred in 29 recipients (16%). PGD grade III developed in 16 of them (55%). The occurrence of PGD grade III was significantly higher in patients needing CPB in comparison with CPB-free recipients \((P < 0.0001)\). Besides, CPB was significantly more often needed in fibrosis patients \((P = 0.001)\).

Overall, PGD grade III occurred in 36 (20%) recipients. One episode or more of acute rejection was identified in 94 (52%) recipients and chronic rejection was diagnosed in 54 (30%) patients. At the end of the study, 84 (47%) patients were still alive and 96 (53%) were deceased: 24 (13%) patients deceased at 1-month post-transplant, 37 (20%) at 3 months and 62 (34%) at 1 year. Mean survival was estimated at 67 ± 5 months with 1-year survival at 66%.

At least, the mean stand back was 2.8 ± 2.9 years. No patient was lost for the follow-up; data on mortality, on acute and on chronic rejections are complete.

We found 30 (16.7%) patients aged <45, 52 (28.9%) aged between 45 and 55, 87 (48.3%) aged between 55 and 65 and 11 (6.1%) patients aged >65. According to the age of recipients, there was no significant difference in the occurrence of PGD grade III or mortality rates.

Patients with PGD grade III had a significantly worse outcome after lung transplantation: survival was significantly lower in those patients \((P < 0.001\); log-rank test). The mean survival was 7.5 ± 1.3 months. Among 36 patients with PGD grade III, 23 (63%) deceased during the first year following transplantation (Fig. 1).

Figure 1: The Kaplan–Meier survival of patients presenting with PGD grade III in the post-transplantation course. A log-rank test compares patients with no PGD grade III in the same period showing a significant difference. PGD grade III group, \(n = 36\); number at risk at 18 months, \(n = 11\). No PGD group, \(n = 144\); number at risk at 18 months, \(n = 90\).

Pair analysis

For each recipient-dependent factor, we extracted pairs opposing both twinned recipient for that factor. Per definition, there were 90 pairs opposing recipients on the side of the lung graft used for transplantation. Thirty pairs (33%) opposed one recipient with fibrosis to an emphysema twin. We also found 24 (27%) pairs opposed on the disimmune medical history, 26 (14.4%) pairs on the pulmonary hypertension, 41 (45.6%) pairs on the former tobacco use, 23 (25.6%) pairs on the need for CPB, 34 (37.8%) pairs on the gender, 18 (20%) pairs on the pregnancy medical history in women opposed to twinned men and 29 (32.2%) pairs on the prior sensitization.

PGD was significantly higher \((P = 0.003)\) in fibrosis recipients opposed to their emphysema twins. Three-month \((P = 0.004)\) and 1-year mortality \((P = 0.004)\) were significantly higher in non-smokers compared with their prior smoker twins.

PGD grade III was significantly higher in patients needing CPB during surgery \((P < 0.0001)\); 3-month and 1-year mortality were also significantly higher in those patients \((P = 0.03\) and \(P = 0.04\), respectively). Survival was significantly worse in the CPB group \((P = 0.04\); log-rank test). One-year mortality was significantly higher in prior sensitized patients \((P = 0.05)\); there was significantly more women and re-transplanted patients in that group \((P < 0.0001\) and \(P = 0.02\), respectively) (Table 3).

Endpoint analysis

We found 28 (31.1%) pairs opposing a PGD grade III recipient to its unharmed twin. The number of pairs opposing twins on 1-month, 3-month and 1-year mortality was 16 (17.8%), 27 (30%) and 38 (42.2%), respectively (Table 4).

The need for CPB during surgery \((P < 0.001)\) and fibrosis \((P = 0.04)\) was significantly more frequent in recipients affected with
PGD grade III compared with their unharmed twins. The mean cold ischaemic time was significantly longer \((P = 0.04)\) in the PGD recipients but overall there was no difference on the number of grafts preserved >360 min. Besides, there were significantly more non-smoker patients affected with PGD grade III \((P < 0.001)\). Performing multivariate analysis, the occurrence of PGD grade III remained significantly higher in fibrosis \((P = 0.036)\) and non-smoker \((P = 0.009)\) patients as well as following the use of CPB during surgery \((P = 0.01)\) (Table 4).

Left single-lung transplantation was significantly higher among patients deceased after 1 month following transplantation. Non-smokers had a significantly worse outcome for 1-month mortality \((P = 0.03)\). Performing multivariate analysis, there was no difference between twins opposed on 1-month mortality (Table 4).

The need for CPB was significantly higher \((P = 0.03)\) in twins deceased 3 months after transplantation. There was no difference on mean ischaemic time but there was significantly more grafts preserved >360 min in the group of deceased patients \((P = 0.04)\). There was significantly more non-smokers among deceased patients \((P = 0.002)\). Performing multivariate analysis, there was significantly more non-smokers among deceased patients \((P = 0.03; \text{Table 4})\).

The need for CPB during surgery \((P = 0.04)\) and medical history of sensitization \((P = 0.05)\) was significantly more frequent among 1 year deceased twins. Non-smokers \((P = 0.006)\) and patients aged over 65 \((P = 0.04)\) were more frequently involved in 1-year mortality. Performing multivariate analysis, patients deceased 1 year after transplantation were more frequently non-smokers \((P = 0.02; \text{Table 4})\).

**DISCUSSION**

The aim of this study was to identify recipient-dependent prognostic factors in a model freed from donor- and transplantation-related factors.
Because of the retrospective and multicentric design of our study, the first step was to assess whether donor and transplantation conditions were comparable for all recipients. Overall, donor quality was similar for all twinned recipients and could be qualified symmetrical within each pair. It is well recognized that extended criteria for donor selection have no adverse influence on outcome transplantation after transplantation [11-13] and have progressively been adopted during the past decade as routine criteria for most transplant teams [14] including in the present French national series.

We did not evaluate the outcome depending on the transplant centre, because we considered that all participating teams had equivalent expertise. Standard single-lung transplantation was performed through a lateral thoracotomy, and all centres followed the usual academic description of the surgical technique. The French ‘Agence de Biomédecine’ evaluated the outcome with reference to the performing centre for the two periods 1998-2002 and 2003-07, using a funnel-plot method. Medium-term survival data of all 10 centres participating in our study remained within the 99% confidence interval (Agence de la Biomédecine. Evaluation d’un indicateur de résultat de l’activité de greffe d’organe en France 2006. Evaluation d’un indicateur de résultat de l’activité de greffe d’organe en France 2009. http://www.agence-biomedecine.fr/article/273).

Immunosuppressive therapy followed the usual recommendations: all 1-month survivors received a standard regimen combining a calcineurin inhibitor (cyclosporine or tacrolimus), an anti-metabolite and corticosteroids [15, 16].

Overall, ischaemic preservation stayed within the limits of 6 h. In each twin pair, both grafts were harvested and preserved with the same preservative. Nevertheless, during the 10 years period of study, there has been a progressive change from intracellular to extracellular preservatives [17, 18]. For our study period, extracellular preservatives such as Celsior” or Perfadex” can be considered adapted [19]; those two solutions were utilized in 88% of all grafts. Changing protocols for organ retrieval and preservation could be considered as a serious limitation of our study; however, the achieved quality of preservation was the same in twinned recipients.

The Eurotransplant study reported a significantly worse outcome after left lung transplantation and when harvest retrieval and transplantation was made by different teams [7]. As opposed, we did not observe any difference in the outcome related to the side of transplantation. As the organization of lung transplantation in France is limited to the national territory, it seldom occurred that harvest retrieval and transplantation were performed by different teams: only 15% (n = 28) of all recipients were in that case.

In our study, 20% of recipients presented with PGD grade III in immediate post-operative course. This is higher than the rate of 10% reported in the international registry [1]. PGD grade III heralded a poor outcome: 1-year mortality in such patients was in excess of 50% (Fig. 1). Therefore, we chose PGD grade III as one of the endpoints.

During the retrieval of data, we strived to be as exhaustive as possible on recipient-dependent factors. In addition to usual demographic data such as gender, age and underlying respiratory disease, we included other factors with potential influence on the outcome such as the disimmune state in the recipient, influence of the respiratory treatment (medication and ventilation) prior to transplantation and sensitization events prior to transplantation. The multiplication of various events and recipient-dependent factors diluted their absolute number; hence, some of them could not be analysed. Parameters were included with the goal to explore recipient-dependent factors that had not been studied before.

Regardless of pair analysis, we found PGD grade III, 3-month and 1-year mortality to be significantly higher in patients with fibrosis. The need for emergency transplantation and CPB was also significantly higher in this group of patients. However, only 12% of patients with fibrosis were on the emergency transplantation list, but twice as much (24%, P = 0.03) needed CPB during transplantation. In twins paired by recipient factors, fibrosis patients opposed to emphysema patients demonstrated a significantly higher occurrence of PGD grade III but there was no difference in mortality. In patients needing CPB during surgery opposed to patients transplanted off-bypass, we found significantly higher PGD grade III, 3-month and 1-year mortality; survival was significantly lower for those patients. Fibrosis was significantly higher in the CPB group.

In twins paired for opposite endpoints, we found significantly more fibrosis than emphysema recipients in those who developed PGD. There was no difference between PGD and non-PGD twins for fibrosis but there was a significantly more emphysema in the non-PGD group. The need for CPB was more frequent in the PGD twins. On multivariate analysis, the need for CPB and fibrosis remained significantly higher in patients with PGD. The only other significant difference we found was in sensitized patients. In pairs opposed on sensitization, 1-year mortality was significantly higher for sensitized patients but lost its significance in multivariate analysis.

We noticed a significantly worse outcome whatever the end-point in non-smokers. This could underline a relationship between the outcome of lung transplantation and underlying respiratory disease. Non-smokers mainly represent fibrosis patients but also patients with a lung disease related to intrinsic factors, compared with chronic obstructive pulmonary disease (COPD) patients in whom respiratory disease is mainly related to extrinsic factors such as smoking.

Overall, we conclude to a strong influence of the underlying respiratory disease on the immediate intra- and post-operative outcomes. Other registry studies have demonstrated a strong relationship between interstitial pulmonary disease and the occurrence of PGD [1]. Obviously, most of these patients present with more or less marked pulmonary hypertension, which could be one of the triggers of PGD. Further, ‘fibrosis’ encompasses a comprehensive group of interstitial lung diseases, suggesting a relationship between interstitial soft tissue abnormalities probably involving immune mechanisms. Owing to small numbers, we could not find any relation between auto-immune diseases and the occurrence of PGD. The influence of fibrosis on PGD grade III was detectable in 3-month and 1-year mortality. Besides, PGD grade III patients demonstrated the overall worse outcome. Twin analysis can confirm fibrosis as a risk factor for PGD as demonstrated before in international registry studies [1].

In parallel, prior exposure to immune sensitizing factors, and not only documented the presence of anti-HLA antibodies, had an influence on the outcome. Eventually, we also had some evidence that intrinsic lung diseases were more likely to lead to the adverse outcome.

To our knowledge, this is the largest study performed on twinned single-lung transplantation. We could not verify some of previous conclusions from similar studies. We found a strong relationship between fibrosis and worse immediate outcome with higher PGD grade III rates. Sensitization events had an adverse
influence with increased 1-year mortality. This kind of study could open the way to risk factor building for lung transplantation but the number of included patients probably still needs to be increased. On the other hand, studying twinned recipients should also enable to identify common factors to twins that have a similar good outcome after lung transplantation.

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REFERENCES

APPENDIX. CONFERENCE DISCUSSION
Dr G.A. Patterson (St Louis, MO, USA): I know how difficult it is to gather data from such a multi-institutional group. This was a thorough and detailed evaluation of this situation in lung transplantation and you, Dr Olland, clearly stated the problem of outcome in transplantation and determinants of that outcome. I think this study reinforces the perception which all of us have had for years that patients with fibrosis don’t do as well in the early perioperative period. Whether this is due to the inevitable technical difficulty of doing a transplant in a fibrotic patient or whether it is due to the frequent need for cardiopulmonary bypass, or perhaps to some recipient inflammatory factors, we do not understand.

I have a couple of reservations about this study, and you may want to comment, Dr Olland, when I am finished, but this is really a relatively small experience. It is the biggest experience of twinned transplant procedures, but we have only 180 transplants done by 10 centres over a period of 10 years, which is a very, very small experience for any individual centre, and I think you are being very generous in assuming that there is no difference between any of those independent transplant centres. I suspect there are probably significant differences between the centres and that may account for the mortality rate. You may have noticed—I am sure the audience appreciated it as well—the relatively high perioperative mortality rate short term, and the very high 1-year mortality rate, particularly in the fibrotic patients. You might want to comment on why it is you think that the results in fibrosis patients are so poor, and whether that perhaps influences the decision and pushes you towards an option for bilateral transplant, where I think the results are superior.

Another question I wanted to ask you, you may want to think about decreasing the size of your sample somewhat, because you have quite a few extraneous groups of patients in there, the number of re-transplants, for example.

Also, I noted from the manuscript, you didn’t comment in the discussion that the flush solution utilized during the period of time was significantly different with, in fact, the majority of patients receiving Celsior® and a very small number of the patients’ lungs being flushed with Perfadex®, which I think most people would argue is the superior flush solution currently in use.

Dr Olland: First, of course this series is very small in comparison to the first series, extended donor criteria in lung transplantation. Curr Opin Organ Transplant 2009; 14: 206–10.

Also, I pointed out in terms of the registries and study registries that have been performed in the past, it is a very small series.

And then looking at our difference between centres, our aim was not to establish if there were big differences, or who was doing it well and who was...
doing it less well. Our principal aim was to have as much twinned single-lung transplantation as possible, in a paradigm where most of the factors would be controlled, and that would be selection of patients, the way surgery was performed, the way full medical follow-up was performed to have a homogeneous way of following up the patients and, of course, having comparable conditions for immunosuppressive therapy.

Looking at the poor results of fibrosis, it has been known by all surgeons performing lung transplantation that fibrosis has a worse outcome compared to other indications, and going up to a bilateral procedure, you usually get better results. This is a tendency now, people more and more retain the bilateral procedure as an indication for fibrosis patients.

And finally, this study has limitations such as the long study period, over 10 years, the fact that it was multicentric in 10 different centres, and of course, over that period, selection criteria for donors weren’t the same, because at the end of the period there were extended criteria. The solution used for pulmoplegia was not the same either: there are more Celsior® preserved lungs than Perfadex® over the study; using the twinned model, the solution would be the same for both grafts and have the same impact on the recipient. The end of the period there were extended criteria. The solution used for pulmoplegia was not the same either: there are more Celsior® preserved lungs than Perfadex® over the study; using the twinned model, the solution would be the same for both grafts and have the same impact on the recipient results. So that was one of the advantages of such a study in the twinned model.

Dr W. Weder (Zurich, Switzerland): I have a problem with your hypothesis where you propose that you are able to study recipient factors in lung transplantation outcome by assuming that the right and left donor lung is of equal quality, and furthermore that the site of the transplantation doesn’t matter. Left and right donor lungs usually have a difference in quality except in the ideal donor. You have aspiration more often on the left side, pneumonias, or you may have contusions to the lungs. Furthermore, transplantation on the left side is not the same as on the right, especially in a fibrotic patient, where the chest cavity is very small and the heart very big due to pulmonary hypertension. So assuming by twinned transplantation that only recipient factors count is not ultimately correct. Could you comment on this?

Dr Olland: Thank you for your question. In fact, with the national registry I could verify first that the lung quality was symmetrical. So there was no aspiration on one side or no contusion on the other side. I really had equal quality for each side and I could assess if there was one side with contusions compared to the other side in the same donor, because that kind of data was present in the national registry. And so I knew in advance if I really had both grafts of equal quality on left and right sides or if I had a difference between those two grafts. Therefore, I was sure even before doing the analysis that both grafts were of equal quality in the same donor. And the step further was then the side analysis. Having equal and symmetrical quality of both grafts, left and right, I could analyse site transplantation and find the result that there was no difference. When you are in the surgical field, there are differences when you perform transplantation, of course.

Dr T. Grodzki (Szczecin, Poland): You cannot ignore the fact that the surgeon is a prognostic factor in transplantation, the team is a prognostic factor. Therefore, I would like to ask you whether the experience of the centres was more or less equally distributed or were there some minor and some bigger centres? This is the first question. Secondly, can you comment on the nonsmokers as a prognostic factor? Because I am trying to understand it myself, but I would like to hear your comment.

Dr Olland: Looking at the centres that were performing transplantation, we didn’t want to compare results between centres. We really wanted to maintain a global study. Of course, some of the centres had larger activity covering a longer period longer compared to others, whose experience with lung transplantation had started maybe a little bit later on, but very comprehensively, all centres are certified centres for lung transplantation, they are accredited by the French Agence de Biomédecine, and they have all been performing lung transplantation as a reference centre.

Regarding the second question on the effect of non-smokers, of course I wouldn’t advise a patient to smoke just before transplantation. There were significantly more fibrosis patients among non-smokers, but also alpha 1 antitrypsin deficiency emphysema patients, patients with lymphangioleiomyomatosis, and that would be all patients with diseases that had an intrinsic mechanism. And that is why I was looking for maybe a further question in my conclusion, is there something like a pathogenic pathway in patients with an intrinsic lung disease and maybe a hyperactive innate immune system that is reflected by the higher grade of PGD. This is the only thought I had about the nonsmoking factor.

Dr N. Shariati (Newark, NJ, USA): I have two short questions for you. One, were the populations matched for presence or absence of pulmonary artery hypertension? Secondly, after the transplant in the fibrotic patients versus your COPD patients, did you have the opportunity to look at episodes of reflux post-transplant, not just presence of reflux preop?

Dr Olland: For pulmonary pressures and hypertension, I didn’t find any differences in the outcome. But, as I said, there is a limitation in the fact that my study was retrospective and there was no homogeneous method for the measurement of pulmonary hypertension. Some of the recipients only had echocardiographic measurement of pulmonary artery pressure, while others had measurement by right catheterization of the heart. So there may already be at that time point a difference between the measurements of pulmonary artery pressure that could explain the fact that I couldn’t find any relevant influence on the outcome of transplantation.

And as for reflux, it is the same. I found some patients with reflux in their medical history before transplantation as well as appearing after. First of all, it wasn’t noticed for all patients, and, second, I didn’t find any influence because I didn’t have enough patients with that characteristic to provide a very relevant or significant analysis on the outcome.