Early lung retrieval from traumatic brain-dead donors does not compromise outcomes following lung transplantation†

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CONCLUSIONS: In our experience, early lung retrieval after brain death from traumatic donors does not adversely affect early and long-term outcomes after LT.

Keywords: Lung transplantation • Lung donors • Brain death • Lung injury • Primary graft dysfunction

INTRODUCTION

Despite the growing interest in lung donation after cardiac death (non-heart-beating donors), brain-dead (heart-beating) donors remain the main source of lung grafts for transplantation. However, only 20% of the multi-organ donors have lungs suitable for transplantation [1]. Brain-stem death induces haemodynamic, neurogenic and hormonal changes that lead to donor lung injury, and is associated with worse graft function in the recipient [2]. Furthermore, it has been demonstrated that the lung is the most vulnerable organ in this setting [3].

Controversial results have been published regarding the possible influence of the cause of death on lung graft function. On one hand, the group of St. Louis reported that traumatic donors were associated with higher incidences of both acute and chronic rejection [4]. Conversely, a multicenter UK Cardiothoracic Transplant Audit revealed no influence of the cause of death on transplant outcomes [5]. Finally, recent ISHLT Registry reports have shown no influence on 1-year mortality, but those recipients receiving lungs from donors dying from anoxia had a decreased risk for 5-year mortality [6].

But the possible influence of the time interval between brain death and organ retrieval on graft function has received little attention from the scientific community. The Group of Newcastle published an experimental model of rat lung transplantation (LT) comparing early and late lung retrieval after brain death. These authors observed that late lung donors presented less damage than early donors, proposing a dominant effect of early haemodynamic damage on the severity of lung reperfusion injury [7].
More recently, the group from Leuven presented an interesting work demonstrating that periods >10 h of brain death before lung retrieval were associated with improved survival, suggesting that the quality of the lung donor may improve as this organ recovers from brain-death-related injury [8].

Taking into account the different time-points of the transplant process, for traumatic patients, the period from brain injury to intubation is usually short (almost simultaneous) and relatively constant. And the period from brain death to organ procurement is also short and quite constant (~8–10 h). Whereas some of these time-points can only be estimated, others are objective. Therefore, we aimed at assessing a period between two objective time-points: patient intubation and donor procurement, and divided this period into early (<24 h) and late (>24 h) lung retrieval (Fig. 1).

With these considerations, the present study was designed to assess whether lung retrieval from traumatic donors performed within the first 24 h of brain injury has a negative impact on graft function and survival after LT, when compared with those retrieved after 24 h.

PATIENTS AND METHODS

Study population

For the purpose of this study, we reviewed the medical records of 356 consecutive lung transplants performed at our institution over a 17-year period. Exclusion criteria were non-traumatic donors (n = 220) and retransplantations (n = 11). On occasion, pulmonary twinning procedures were done, so both lungs of a single donor were transplanted into two separate recipients. Thus, a total of 132 transplants entered in the analysis. There were 53 (40%) single lung transplants (SLT), 77 (58%) double lung transplants (DLT), 1 combined liver-LT (1%) and 1 combined heart-LT (1%).

Lung donor assessment and procurement

Donors and recipients were matched for blood groups and thoracic dimensions measured from chest radiographs and predicted total lung capacity. Lung donor procurement was performed following the standard technique of combined cardiopulmonary extraction [9]. At the time of median sternotomy, the donor was given 10 mg/kg methylprednisolone (Solu-moderin®, Pharmacia & Upjohn, Barcelona, Spain). After the heart and lungs were dissected free, the donor was pretreated with intravenous heparin (300 U/kg). The aorta and main pulmonary artery (PA) were each cannulated in turn, and 1 mg of prostaglandin E1 (Alprostadil® 500 mcg/ml, Pfizer Manufacturing Belgium NV/SA, Belgium) was administered directly into the donor main PA before cross-clamping the aorta. The lungs were flushed antegradely via the main PA, venting the perfusate through the left atrial appendage. Throughout the period of perfusion and removal, the lungs were ventilated at tidal volume (FiO₂ < 1) and topically cooled. On completion of the perfusate, the heart was removed first, the trachea was double-stapled and transected, and the lungs were removed at end-tidal inflation. Immediately after lung harvesting, an additional retrograde flushing through the pulmonary veins was performed to optimize lung preservation by perfusing the bronchial circulation [10]. The lungs were preserved by immersion at 4°C for transportation to our institution. The preservation solution used was modified Eurocollins® (60 ml/kg; 4°C, 30 cm H₂O) until year 2001, and Perfadex® solution (Vitrolife, Gothenburg, Sweden) thereafter.

Operative technique

Either single-or double-LT was performed in the recipient through a posterolateral thoracotomy or a Clam-shell incision, respectively. On completion of the bronchial anastomosis, the PA and the left atrium were anastomosed in a standard fashion. Cardiopulmonary bypass was instituted in case of inability to maintain the recipient on one-lung ventilation during the pneumonectomy of the native lung or implantation of the graft, or in case of graft dysfunction after the first lung was implanted. At the end of the procedure, a fiberoptic bronchoscopy was performed to assess the viability of the bronchial anastomosis and to aspirate secretions in the airways.

Postoperative management

Patients were ventilated until they were able to maintain both adequate gas exchange and tidal volumes. We aimed at achieving the weaning from mechanical ventilation within the first 48–72 h post-transplantation. Immunosuppression consisted of the standard triple-therapy regimen. Antimicrobial therapy was administered based on antibiotic sensitivities from preoperative sputum cultures of the recipient and from the donor.

Figure 1: Time-points of the process of donation and lung procurement.
Bronchoaspirate. Acute rejection episodes were diagnosed by clinical criteria and transbronchial lung biopsy in the absence of positive bronchoalveolar lavage cultures, and were treated with bolus doses of methylprednisolone (10 mg/kg/day) for 3 consecutive days. Bronchiolitis obliterans syndrome (BOS) was diagnosed by transbronchial lung biopsy and/or when no other explanation for persistent declines in FEV₁ could be found.

**Definitions**

Primary graft dysfunction (PGD) was defined following the Statement of the International Society for Heart and Lung Transplantation (ISHLT) [11]. Table 1 shows grading of PGD severity according to the ISHLT Working Group on PGD. Patients with PGD grades 2 or 3 at 72 h post-transplant were considered for the analysis.

BOS, as the functional definition of chronic rejection, was graded according to the ISHLT Classification of 2003 [12], and patients with BOS grades 2 or 3 were included in the analysis. BOS classification used for this study is depicted in Table 2.

Extended donors were defined as those having at least two of the following criteria: age >55 years, chest X-ray with mild infiltrates, tobacco history >20 pack-years, moderate secretions at bronchoscopy or mild pulmonary contusion. Nevertheless, donors with oxygenation ratios <300 mmHg were not considered for transplantation in any case [13].

**Data collection, endpoints and statistics**

All data were collected retrospectively. Donor-related variables included gender, age, ABO blood group, PaO₂/FiO₂ at the time of organ retrieval, duration of mechanical ventilation, Intensive Care Unit (ICU) stay, the cause of death and the use of extended donors. Preoperative recipient variables included age, gender, ABO blood group and transplant indication. Intraoperative variables were the type of transplantation, the need for cardiopulmonary bypass and the ischaemic time of the first and second lung grafts. Postoperative variables included PaO₂/FiO₂ ratio within the first 24 postoperative hours, duration of mechanical ventilation, acute rejection episodes (overall, within 1 month post-transplant, between 2 and 3 months post-transplant and after 3 months post-transplant), freedom from BOS, 30-day mortality and survival.

Patients were distributed into Group A, which consisted of the recipients who received lungs retrieved within the first 24 h after brain injury; and Group B, which consisted of those who received lungs retrieved after 24 h of brain injury. The influence of early (<24 h) vs late (>24 h) retrieval on the development of PGD, rejection episodes, freedom from BOS, 30-day mortality and survival was studied.

Univariate analysis was used to compare the influence of each donor variable on the development of PGD, acute rejection episodes, BOS and survival. Continuous data were assessed for normality and presented as mean ± SD with 95% CI. Normally distributed variables were compared using unpaired Student's t-test. For non-parametric distribution, Mann-Whitney U-test was used. Categorical data were analysed using Pearson's χ² test and Fisher's exact tests. Survival data were calculated by Kaplan-Meier analysis and log-rank test. Statistical significance was assigned at P < 0.05. Data were analysed using the SPSS 12.0 software (SPSS, Inc., Chicago, IL).

**RESULTS**

One hundred and thirty-two lung transplants from traumatic donors were analysed. Main indications were chronic pulmonary obstructive disease (COPD) in 41 (31%), cystic fibrosis in 38 (29%), pulmonary fibrosis in 31 (23%), bronchiectasis in 9 (7%) and other indications in 13 patients (10%). Donors were 100 males (76%) and 32 females (24%), with a mean age of 24 ± 11 (7–61) years.

Comparative data between Groups A and B are depicted in Table 3. Seventy-three patients (55%) were included in Group A and 59 (45%) in Group B. There was a slight male-to-female predominance among traumatic lung donors in both Groups A and B, though not significant (P = 0.466). Of note is that donors from Group B were younger (22.1 ± 9.1 years) than those from Group A (26.2 ± 12.1 years, P = 0.027), and were obviously intubated for longer periods (67.1 ± 44.7 vs 20.4 ± 4.6, P < 0.001). Also, recipients from Group B developed more acute rejection episodes within the first postoperative month, than those of Group A (0.83 ± 0.7 vs 0.48 ± 0.5, P = 0.007). Other factors such as donor oxygenation, ischaemic times, recipient oxygenation at ICU admission and postoperative intubation did not differ between groups. Also, no differences were found in the use of extended donors, recipient diagnosis, type of transplant and the need or cardiopulmonary bypass (Table 3).

**Mortality**

The overall mortality was similar in both groups: 40 patients (55%) died in Group A, compared with 38 (64%) in Group B, P = 0.29. Non-cytomegalovirus (CMV) infection and BOS together caused

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**Table 1:** Grading of PGD severity

<table>
<thead>
<tr>
<th>PGD grades</th>
<th>PaO₂/FiO₂</th>
<th>Rx infiltrates (oedema)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;300</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>&gt;300</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>200–300</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>&lt;200</td>
<td>Present</td>
</tr>
</tbody>
</table>

ISHHLT Working Group on Primary Lung Graft Dysfunction [11]. Patients showing PGD grades 2 or 3 at 72 h post-transplantation were included in the analysis.

**Table 2:** BOS classification according to the ISHLT statement of 2003 [12]

- **BOS 0**: FEV₁ > 90% of baseline and FEV₂5–75 > 75% of baseline
- **BOS 0p**: FEV₁ 81–90% of baseline and/or FEV₂5–75 ≤ 75% of baseline
- **BOS 1**: FEV₁ 66–80% of baseline
- **BOS 2**: FEV₁ 51–65% of baseline
- **BOS 3**: FEV₁ ≤ 50% of baseline

BOS grades 2 or 3 post-transplantation were considered for the analysis.
two-thirds of all deaths in our series (28 and 21 patients, respectively). Less frequent causes were PGD (7 patients, 10%), cardiac complications (7 patients, 10%), surgical (5 patients, 7%), CMV infection (3 patients, 4%) or acute rejection episodes (3 patients, 4%). However, these differences were not significant. Some individuals developed more than one complication. When analysing 30-day mortality, only 2 patients (3%) from Group B died within the first 30 days post-transplantation, as opposed to 7 (10%) in Group A, but these differences were not statistically significant (Table 3).

### Primary graft dysfunction

The overall incidence of PGD grades 2 or 3 at 72 h post-transplant was 17% (95% CI, 10–23%) (22 recipients). There were no differences in the development of PGD between Groups A and B, although up to 26% of patients (n = 13) in Group B developed PGD compared with 9 patients (16%) in Group A (P = 0.17) (Table 3).

### Survival

Comparative survival curves for the two groups are illustrated in Fig. 2. Overall survival in our series showed a half-life of 5.7 years for Group A, and 5 years for Group B, without statistically significant differences (P = 0.93) (Fig. 2A). When we analysed the survival, conditional to survive 1 year, the probability of survival continued to be similar between groups, with a half-life of 11.5 years in Group A and 12.8 years in Group B (P = 0.99) (Fig. 2B).
5, 10 and 15 years, respectively. These data did not differ between groups neither in the overall series (Fig. 4A, \( P = 0.88 \)), nor when analysing only those patients surviving the first year post-transplantation (Fig. 4B, \( P = 0.91 \)).

**DISCUSSION**

The present study demonstrates that early lung retrieval from traumatic donors performed within the first 24 h after brain injury is not associated with worse graft function and in-hospital outcomes following LT. In addition, mid- and long-term survival are not compromised by the use of these grafts. However, we found that transplantation of grafts from early-retrieved traumatic donors to fibrotic recipients was associated with worse 5-year survival.

To date, brain-dead donors remain the main source of grafts for transplantation. However, brain death is associated with inferior graft function after kidney, liver, heart or LT. The lung is especially vulnerable and may not manifest injury until the post-transplant period. Various groups have investigated the impact of donor’s cause of death on LT, with conflicting results. Waller et al. [14] found that the use of donors involved in major trauma does not affect the duration of postoperative mechanical ventilation, the \( \text{PaO}_2/\text{FiO}_2 \) ratio at 24 h post-transplantation, or the 30-day mortality rate. Ciccone et al. [4], from Washington University, demonstrated equivalent early outcomes and no significant difference in long-term survival between traumatic and non-traumatic donors, although recipients receiving lungs from traumatic donors had higher risk for BOS and more severe acute rejection episodes. Furthermore, a UK Cardiothoracic Transplant Audit, using data from a national prospective cohort study of adult single and bilateral lung transplants [5], could not find an association between donor cause of death and mid-term survival after LT. Conversely, Singhal et al. [15] analysed the impact of donor cause of death on outcomes following solid organ transplantation, using data of the UNOS Registry. They found that stroke was associated with worse recipient outcomes compared with head trauma. On the contrary, lungs transplanted from donors with anoxia showed the best survival and less rejection.

Whereas some authors have argued that organs from brain-dead donors should be retrieved early before further damage occurs by the progressive systemic inflammatory response [16], others like the group of Newcastle [7], suggested that delaying lung procurement might be of benefit, because the initial subclinical injury may improve with time as the potential donor is resuscitated and stabilized. The latter investigated the contribution of the brain-death-induced donor lung injury to PGD after pulmonary reperfusion. This group developed a rat LT model in which they compared early lung recovery (after 15 min of brain death) with late recovery (after 5 h), and found that late retrieval was associated with lower pulmonary vascular resistance, and not with inferior graft function or higher levels of inflammation. The authors suggested that the lungs might improve with time after the sympathetic storm in the donor [7]. Translating this into the clinical scenario, Wauters et al. [8] investigated the influence of donor cause of death and related time intervals on survival and freedom from BOS after LT. Cause of donor death was classified into vascular, traumatic and other (tumour, hypoxia, metabolic and infection). Time intervals from brain injury to brain death (BI-BD) and from brain death to cold preservation (BD-CP) were compared among groups. They found that the

**Bronchiolitis obliterans syndrome**

Kaplan–Meier estimates of freedom from BOS were 82, 72, 37 and 22% for Group A and 78, 68, 42 and 15% for Group B, at 3,
cause of death was not associated with hospital mortality or survival, but recipients from donors with an interval BD-CP >10 h experienced an improved survival. The authors suggested that the quality of the donor lung could improve with a longer time interval that elapsed between the sympathetic storm in the donor and cold perfusion.

In accordance with previously published studies [6], we found a slight male-to-female predominance among traumatic lung donors in both Groups A and B, though not significant. Traumatic donors are more often male because males more frequently are affected by trauma, compared with females who die from cerebrovascular disease.

It is noteworthy that donors from Group B were significantly younger than those from Group A. One should expect less co-morbidities in young donors compared with old donors, and this might explain why the former are intubated for longer periods before the declaration of brain death as opposed to the latter. It is obvious that donors from Group B were intubated for longer periods as the defining criterion for this group was lung retrieval after 24 h of brain injury.

Our incidence of PGD is similar to the data provided by the ISHLT report [6]. There was a trend of increased occurrence of PGD in Group B relative to Group A. Thus, up to 26% of patients in Group B developed PGD compared with 16% in Group A.
though this is not significant. Nevertheless, no differences in PaO2/FiO2 levels in the donors were found when stratifying between early and late lung harvesting (Table 3). Consequently, one can speculate that lungs retrieved late showed worse function in the recipient because during the time that elapsed from the declaration of brain death to lung procurement, the donor was not properly managed.

Incidence of acute rejection episodes appeared to be different between early and late donors, as shown in Table 3. One possible mechanism that might explain this finding could be the delay in lung harvesting following traumatic brain death, but to date this explanation remains hypothetical and warrants further investigation.

No difference could be found between early or late lung retrieval and freedom from BOS, neither in the overall series (Fig. 4A), nor when analysing only those patients surviving the first year post-transplantation (Fig. 4B). Freedom from BOS was 82, 72, 37 and 22% in Group A and 78, 68, 42 and 15% in Group B, at 3, 5, 10 and 15 years, respectively. These findings are in accordance with the results published by Wauters et al. [8]. Further, a multicenter UK Cardiothoracic Transplant Audit [5] including 580 lung transplants revealed no influence of cause of donor death and development of BOS. On the contrary, Ciccone et al. [4] found a higher incidence of BOS in recipients from traumatic donors relative to non-traumatic donors.

Overall survival in our series showed a half-life of 5.7 years for Group A, and 5 years for Group B (Fig. 2A). For those recipients surviving the first year post-transplantation, the probability of survival continued to be similar for the two groups (Fig. 2B). On the contrary, when we analysed survival stratifying by transplant indication, we found a trend of reduced survival among fibrotic recipients when they received lungs retrieved early (Group A), compared with CF and COPD recipients (Fig. 3). However, these differences were not significant, probably due to the fact that there were no long-term survivors in Group B. Current 1-, 5- and 10-year survival rates for pulmonary fibrosis are 74, 45 and 22%, respectively, which are significantly worse than those for other causes of end-stage lung disease undergoing LT. This emphasizes the idea that high-risk recipients like those IPF patients should receive lungs from ‘ideal’ donors, and perhaps late retrieval from traumatic donors is not the best strategy for fibrotic recipients.

There are some limitations of our study. First, the design of the study is retrospective. Thus, introduction of a bias is not excluded. Secondly, even if the number of patients included in the study is important, it is likely that we lacked the statistical power to detect differences between both groups. Thirdly, the definition of PGD has changed over time. Using the last Grading of PGD severity of the ISHLT Working Group [11], we had to re-code this variable following the new criteria. It is possible that more deaths attributable to PGD than observed could have occurred, but given the retrospective nature of the study, we were afraid of changing the recipient’s cause of death. And last, the fact that we could not find an association between early lung retrieval and worse results after LT may indicate that, in our setting, delaying lung donor procurement might not be of benefit if this time elapse is not followed by an aggressive management of the potential donor that could result in improved graft function and survival of the recipient.

In summary, early lung retrieval from traumatic brain-dead donors does not adversely affect early and long-term outcomes after LT for COPD and cystic fibrosis. On the contrary, transplantation of grafts from early-retrieved traumatic donor lungs to fibrotic recipients might be associated with poor 5-year survival. Therefore, active and early management of any potential lung donor is always advisable. Failure to follow these recommendations could result in worse survival after LT, especially for fibrotic patients. Further research is required to provide the clinical relevance of this finding.

Conflict of interest: none declared.

REFERENCES


