Lung transplantation using donors 55 years and older: is it safe or just a way out of organ shortage?☆

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Abstract

**Objectives**: Lung organ scarcity has led to more generous acceptance of organs under the idea of extended-donor criteria. However, long-term effects have to be monitored to redefine present practice. In this study, we investigated the impact of donor age over 55 years in lung transplantation. **Methods**: In this retrospective study, 186 consecutive double-lung transplantation procedures from January 2000 to December 2008 were evaluated. A total of 19 recipients received lungs from donors aged 55 years or older (range 55-69 years) (group A) and 167 received lungs from younger donors (range 8-54) (group B). In-hospital mortality, intensive care unit (ICU) stay, rejection episodes, lung function and survival up to 5 years were evaluated. **Results**: In-hospital mortality was similar in both groups (group A: 10.5%; group B: 13.7%). Postoperative ICU stay was 19 ± 33 days versus 17 ± 34 days (A vs B). Rejection episodes as well as postoperative lung function up to 5 years, and overall cumulative 5-year survival (group A: 52.4%; group B: 50.9%) did not reach statistical significance. However, a trend of increased bronchiolitis obliterans syndrome (BOS) prevalence and reduced lung function was noted. Cause of death showed no differences in both groups. **Conclusions**: Donor age ≥55 years does not compromise immediate and long-term results after lung transplantation, although long-term observation of patients receiving such an organ suggests earlier lung dysfunction. Due to the rising need of organs, lungs from donors aged 55 or older have to be considered for transplantation. However, the acceptance should be based on donor lung evaluation and individual recipient needs. Long-term outcomes over 5 years need to be further investigated.

1. Introduction

Lung transplantation has evolved to a recognised therapy of terminal end-stage lung disease. With the transplantation procedure established in many centres and countries, the number of eligible patients is constantly growing. However, the scarcity of lung donors has clearly limits this option, leading to an increasing waiting time as well as to a growing mortality of patients on the lung transplant waiting list, reaching up to 20% [1].

Faced with this problem, lung transplantation centres have started expanding their criteria for the acceptance of lung organs as a way to increase the use of lungs in multi-organ donors, which currently lies at just about 20–30% in the Eurotransplant community (Eurotransplant Report 2007).

Simultaneously, different practices as living-donor transplantation and the use of non-heart-beating donors have been established to expand the number of available lung organs, but are still limited by technical, medical and ethical considerations [2,3]. Continued research helps in understanding the different mechanisms of preservation, ischaemia/reperfusion injury, progression of the bronchiolitis obliterans syndrome (BOS) and the effect of different variables in the donor. Despite all these efforts, organ shortage still represents one of the major problems worldwide.

Lung transplant centres have to carefully weigh the options for each patient, often under pressure because of the urgent need of transplantation and the lack of suitable organ offers. Despite these circumstances, current practice has to be critically analysed to achieve the best therapy possible for the patients.

The criteria for lung organ acceptance as known in the early era of transplantation have evolved to try to meet the centres’ need for organs. The criteria comprise: (1) donor age <55 years, (2) pO2 > 300 mmHg at 1.0 FiO2, (3) length of donor mechanical ventilation <5 days, (4) no purulent secretion on bronchoscopy, (5) absence of infiltration on chest X-ray (CXR) and (6) absence of chest trauma [4]. The
tolerance of any of these recommendations has led to differentiation of ideal and extended donors [5–7]. In the past years, every criterion of the original list has been extended with fairly good results [7]. However, donor age still plays a role in the subjective acceptance of lung organs without evidenced negative effect on the short-term outcome and/or postoperative course [8, 9]. Concerns have arisen because of the negative effects in long-term results with increased observation of BOS and mortality after more than 5 years [1, 10]. In addition, donor age >35 years appears as a relative risk for 5-year mortality in the International Society for Heart and Lung Transplantation (ISHLT) registry report [11].

Therefore, the aim of this study was to investigate the impact of donor age ≥55 years in the lung transplantations performed in our institution.

2. Patients and methods

The lung transplantation programme of our centre started in the year 2000 with seven performed procedures and steadily increased up to 36 procedures (single- and double-lung transplantation) performed in 2008. Lung organ donors ≥55 years began to be accepted in the year 2003 and their use increased every year, reaching a maximum in 2008, where six double-lung recipients out of 37 (16%) were transplanted with an organ donor ≥55 years.

2.1. Patients

Between January 2000 and December 2008, 186 consecutive double-lung transplantations were performed at our institution and analysed retrospectively from our database. The mean recipient age was 51.5 years (range 16–66 years) and the female gender prevalence was 47.9%.

2.2. Donor acceptance

All donors were assessed for acceptability for transplantation by the lung transplant surgeon on duty from our institution. Donor management was performed from the time point of acceptance until retrieval following our institutional protocol: (1) bronchoscopy by local doctor, (2) no crystalloid infusions, (3) diuretics intravenously, if needed, (4) haemoglobin >10 mg dl⁻¹, (5) central venous pressure 5–10 cm H2O, (6) tracheal cuff blocked at maximum, (7) maximum inspiratory pressure 25 mmHg, PEEP 8 cm H2O and (8) single-shot intravenous antibiotic (preferably fluoroquinolones). Before arrival of the explantation team, donor management was performed by personal communication with the coordinator on-site, including sending our protocol by fax whenever possible.

Donor lungs were assessed after first screening of documentation and then by on-site bronchoscopy and sighting of CXR by the retrieving surgeon. Macroscopic inspection and palpation were finally performed and final acceptance occurred after evaluation of the perfused lung grafts.

Lung function before harvest was based on the final pA02/FiO2 ratio in the operating room after implementation of our protocol, including adjustment of mechanical ventilation and performance of bronchoscopy by the transplant surgeon. Lung procurement and preservation followed standard procedures with cold low-potassium-dextran solution for anterograde and retrograde flushing.

2.3. Lung transplantation procedure and postoperative care

All double-lung transplantations were performed with standard use of cardiopulmonary bypass (CPB). Immunosuppression was based on a triple therapy (cyclosporine, mycophenolate mofetil and prednisolone). Prophylaxis for Pneumocystis carinii and cytomegalovirus infection was achieved with low-dose oral trimethoprim-sulfamethoxazole and intravenous gancirolvir, respectively. Standardised evaluation for rejection and infection included clinical assessment, CXR and pulmonary function test. Diagnostic bronchoscopy was performed daily in the immediate postoperative period and was performed subsequently for clinical symptoms or spirometric evidence of allograft dysfunction. In-hospital mortality was defined as mortality during complete postoperative stay.

Surveillance monitoring, including spirometry, bronchoscopy and trans-bronchial biopsies, were performed after 3, 6, 9, 12, 18 and 24 months in the absence of symptoms in our transplantation clinic, afterwards in yearly intervals.

2.4. Database

All data acquired during the patients’ surveillance were transferred to our institutional database. Data entered could be retrieved at any time by transplantation personnel with filtering and sorting as needed.

2.5. Statistical analysis

Statistical analyses were performed using SAS V. 9.1 (SAS Inc., Cary, IL, USA). Continuous data were expressed as mean ± standard deviation (SD); categorical data were expressed as percentage. Comparisons between two groups were carried out using unpaired Student’s t-test for normally distributed data or the Mann–Whitney rank sum test for non-normally distributed data. Multiple groups were compared with analysis of variance (ANOVA). Correlations were calculated with Pearson’s product moment correlation or with Spearman’s rank order correlation, depending on skewness and distribution of data. The probability of observed numerical variables was determined with Fisher’s exact test. The survival rates of patients were estimated with the Kaplan–Meier product-limit method including stratified analyses. A p value of less than 0.05 indicated statistical significance.

3. Results

3.1. Donor and recipient data

A total of 19 recipients (10.2%) received an organ from a donor aged ≥55 years (group A) in contrast to 167 recipients (89.8%) of organs from younger donors (group B).
Donor characteristics did not differ significantly in the observed groups (Table 1). The median age was 57 years (range: 55—69 years; 84% female) in group A in contrast to 41 years (range: 8—54 years; 56% female) in group B. The functional status as described by the oxygenation capacity, as well as the typical risk factors — chest trauma, smoking history and purulent secretion at bronchoscopy — showed no discrepancy between the groups. Moreover, no correlation between donor age and donor oxygenation capacity could be detected; arterial partial oxygenation pressure at 100% oxygen flow showed a similar distribution (Fig. 1). Ventilation time until organ explantation and thoracic X-ray displayed no significant repartition between the groups. The cause of death displayed a typical distribution with intra-cerebral bleeding as the main cause, followed by traumatic injury and hypoxic brain injury (Table 1).

Recipient data showed similar values in both groups (Table 2). The median age of recipients was 53 years (range 35—62 years; 63% female) in group A versus 51 years (range 16—66 years; 46% female) in group B. Indications for lung transplantation were mainly lung emphysema, pulmonary fibrosis and cystic fibrosis. High-urgency status at the time of transplantation was granted in 58% of patients in group A and in 59% of the patients of group B. Preoperative mechanical ventilation was present in 21% of the patients of group A and 12% of the patients of group B.

### 3. Parameters after lung transplantation

All values are displayed in Table 4. Intra- and postoperative data including ischaemia time, time on CPB and initial oxygenation capacity of the transplanted lungs was similar. The duration of postoperative mechanical ventilation indicates a higher mean in the younger donor group but did
not reach statistical significance. Length of intensive care unit (ICU) stay and hospital stay showed no significant differences, although a trend to longer mean of hospital stay was noted in group A as shown in the 95% confidence interval.

In-hospital mortality was similar (group A: 10.5%; group B: 13.7%; n.s.).

Spirometry data up to 5 years displays a stable function among transplanted patients in both groups. However, a trend of lower percentage in the mean is seen from 36 months postoperatively in the donor group ≥55 years, displayed by the confidence interval, not reaching statistical significance (Table 4).

The occurrence of BOS of any grade after 5 years was documented in 42% of patients in group A versus 32% in group B, without reaching significance. Rejection episodes with the need for steroid therapy occurred in 16% of the patients of group A and in 22% of the patients of group B. Cause of death did not show any significant difference between groups (Table 3).

### Table 3

<table>
<thead>
<tr>
<th>Cause of death (n = 61)</th>
<th>Group A (n = 8)</th>
<th>Group B (n = 53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis/multi-organ failure (n/%)</td>
<td>4 (50%)</td>
<td>29 (55%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Acute graft failure (n/%)</td>
<td>1 (12.5%)</td>
<td>7 (13%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bleeding (n/%)</td>
<td>1 (12.5%)</td>
<td>2 (4%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiac/haemodynamic complications (n/%)</td>
<td>1 (12.5%)</td>
<td>6 (11%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Carcinoma (n/%)</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Neurological complications (n/%)</td>
<td>1 (12.5%)</td>
<td>6 (11%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

### Table 4

Outcome after lung transplantation.

<table>
<thead>
<tr>
<th>Age ≥55 years (n = 19)</th>
<th>Age &lt;55 years (n = 167)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB-time (min) [95% CI]</td>
<td>229 ± 42 [210–248]</td>
<td>220 ± 56 [212–228]</td>
</tr>
<tr>
<td>Ischaemic time right lung (min) [95% CI]</td>
<td>281 ± 50 [258–304]</td>
<td>267 ± 63 [257–277]</td>
</tr>
<tr>
<td>Ischaemic time left lung (min) [95% CI]</td>
<td>353 ± 40 [335–371]</td>
<td>326 ± 70 [315–337]</td>
</tr>
<tr>
<td>Length of ICU stay (day) [95% CI]</td>
<td>19 ± 33 [4–34]</td>
<td>17 ± 34 [14–20]</td>
</tr>
<tr>
<td>Length of hospital stay (day) [95% CI]</td>
<td>42 ± 31 [28–56]</td>
<td>33 ± 23 [28–38]</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio (mmHg) Initial (on arrival on ICU) [95% CI]</td>
<td>577 ± 210 [482–672]</td>
<td>432 ± 212 [400–464]</td>
</tr>
</tbody>
</table>

**Spirometry**

| FEV1 (%) at hospital discharge [95% CI] | 66 ± 15 [59–73] | 63 ± 18 [60–66] | n.s. |
| FEV1 (%) 6 months [95% CI] | 67 ± 18 [59–75] | 74 ± 25 [70–78] | n.s. |
| FEV1 (%) 12 months [95% CI] | 71 ± 24 [60–82] | 74 ± 26 [70–78] | n.s. |
| FEV1 (%) 36 months [95% CI] | 59 ± 28 [47–71] | 73 ± 30 [68–78] | n.s. |
| FEV1 (%) 60 months [95% CI] | 55 ± 25 [44–66] | 75 ± 28 [71–79] | n.s. |

### 3.3. Survival

No significant difference could be achieved in the overall cumulative 1-, 3- and 5-year survival between both groups (Fig. 2). Five-year survival appeared with 52.4% and 50.9% in the elder donor group and younger donor group, respectively.

### 4. Discussion

In our experience, the intra- and postoperative data suggest no significant differences in the outcome and handling of lung-transplanted patients with organs from donors ≥55 years old. Only bilateral lung transplantations were considered since single-lung transplantation as well as heart–lung transplantation do differ in long-term follow-up when compared with double-lung transplantation [12]. Organ implantation was always performed under CPB support as, in our experience, the occurrence of ischaemia/reperfusion injury in general is clearly diminished. The use of CPB for lung transplantation is still under debate. However, the reported advantages consist of safeguarding circulation and gas exchange of the recipient, preventing
early hyperperfusion of the first implanted graft and, most importantly, controlling reperfusion and ameliorating ischaemia/reperfusion injury to both implanted grafts [13,14]. Therefore, perioperative factors were similar in both groups, excluding the influence of different strategies on the long-term outcome of both groups.

The oxygenation capacity of the donor lung did not show any difference depending on donor age above or below 55 years (Fig. 1). Lung function after transplantation was excellent in both groups as evidenced by the postoperative oxygenation values and spirometry. A non-significant decline in forced expiratory volume (FEV1) was noted after 3 years in group A when compared with group B. BOS development showed a trend of increased occurrence within 5 years of follow-up in group A when compared with group B, without reaching significance.

The 5-year cumulative survival rates of 52% and 50% in the older donor group and in the younger donor group, respectively (Fig. 2), are similar to the data provided by the ISHLT registry (53.5%) [11], and provide evidence of benefit for the patients, especially when considering mortality rates of up to 20% without transplantation while waiting on the list [1].

In our centre, the selection of donors ≥55 years was always decided in the same manner as for donors <55 years by the transplantation team on duty. The early preoperative management based on our institutional protocol and the evaluation on-site proved to be of high value. The age-independent acceptance of the lung is reflected by the donor and recipient characteristics: in both groups, traditional exclusion criteria such as infiltrations in CXR, smoking history, purulent secretions in bronchoscopy and chest trauma were present in the same amount. In addition, recipients of lungs from older donors were not older as were the recipients of younger donors, neither was there a difference in the number of patients urgently requiring the transplant in both groups, excluding the reported ‘old for old’ or the ‘old for critical patients’ concept. Finally, ischaemia time was comparable in both groups, ruling out short transportation time/distance as a factor leading to the increased use of older donors. Therefore, the result observed of similar outcomes after lung transplantation from donors ≥55 years and donors <55 years reflects critical organ evaluation.

The main findings of our analysis are consistent with experiences reported by other groups [1,8,9,15,16]. The use of donors ≥55 years or even 60 years is generally supported due to the overall comparable 5-year survival, but reports of increased BOS occurrence and a lower 10-year survival may represent a serious issue, which has to be taken into consideration [1]. Our data do not permit any statement regarding 10-year follow-up, but beginning lower spirometry values and rising occurrence of BOS after 5 years could indicate the beginning of graft dysfunction beyond the observation period. Furthermore, the observation of increased mortality has been reported when ischaemic time exceeds 7–8 h as well as when recipient age was above 55 years [16]. Further studies need to investigate the effect of age on the lung itself and the following resulting impairments after an ischaemia/reperfusion injury and transplantation. Different factors could influence the tolerability of the lung before, during and after transplantation. All these considerations should be taken into account, but present data are insufficient to advise against the use of older donors, since the benefit for the patient still overrides any doubts that may exist.

The increasing use of extended-donor organs raises ethical questions concerning the need of information up to the need of consent of the recipient. In addition, transplant centres are confronted with the decision of accepting extended-donor organs only for highly urgent cases or for all recipients. The extended criteria, including donor age, do not seem to affect immediate results after transplantation and long-term effects have yet to be proven. Therefore, in the times of organ shortage, all transplantable organs should be used after thorough inspection.

Our retrospective analysis exhibits some limitations; first, there is a small number of lung donors aged 55 years or above who have been used for transplantation in the observed time interval from the year 2000 to 2008. Second, the retrospective aspect of our study does not consider all the potential older donors, which have not been used for transplantation. The observations made in this article may be biased by pre-selection of older donors, artificially affecting the results after transplantation.

Until new insights are offered, lung donors aged above 55 years have clearly to be considered as suitable graft donors and the age of the donor should play a secondary role. Lung graft assessment should be based on the observations of an experienced transplant physician, both on paper and in the operation room, with the acceptance based on all parameters of the lung and the individual recipient’s needs.

References


Appendix A. Conference discussion

Dr I. Kron (Charlottesville, Virginia, USA): Clearly the authors have shown that there is no issue with using these donors, though there was a tendency towards bronchiolitis obliterans. We are going to report in about two weeks on a very large UNOS database looking at freedom from bronchiolitis obliterans, and donor age does not seem to be an issue, even at 10 years. So I think that these probably will be very safe.

I have two questions for you. One, you got us up to age 69. What about above that now? There may be some perfectly good donors there. Secondly, you did mention that you did not preselect this. As you know, there is a lot of heart transplant literature using worse donors for worse recipients, and your strategy has been different. What patient would you not use an older donor in, someone who is 18 with cystic fibrosis? Perhaps you can comment on that as well.

Dr Pizanis: How old can the donors get? This is a very interesting question that we have thought about, too, and I can tell you that the 69-year-old donor that we took, we evaluated him probably twice as much as usual, and maybe answering the second question with it, it was for a young 36-year-old patient with cystic fibrosis, high urgency, and this patient was waiting for a pretty long time, so we thought it is now or never. Now, it’s very difficult to say when to do something and when not. I think age should be secondary in donors. We have to evaluate the lung with our experience, we have to look at the function, we have to weigh the lungs, look to see if everything is all right, and then, again, with experience, subjectively decide if the patient has to get it or not. I’m not a fan of saying that you have to take older donors for older recipients or whatever, but this topic is very difficult, and the main problem is that every centre decides on its own and no central experience database has been established until now.

I see Dr Stueber, who has a lot more experience.

Dr M. Stueber (Hannover, Germany): I do have a problem with your data analysis. Your subset of older donors is just too small to do any sensible statistics with, just 19 cases. So saying that it’s not statistically different, it doesn’t make much sense in this context. But if you look at what you really did, then it becomes very interesting: you have some bias in your data, because I noticed just one case of cystic fibrosis recipient in your older donor group, and you used more than 80% female donors in your older donor group. So there is a bias in your selecting criteria, and I think that is the interesting message, that you go into this older donor group and do a real selection of these patients to be successful with the lung transplantation. I think we have to develop some guidelines, some ideas of how to better select donors in the older age group to make it a successful organ transplant.

Dr Pizanis: I agree with that.