The use of non-heart-beating lung donors category III can increase the donor pool

Caroline Van De Wauwer, Erik A.M. Verschuuren, Wim van der Bij, George D. Nossent, Michiel E. Erasmus

Abstract

Objective: The use of non-heart-beating (NHB) lung donors has been propagated as an alternative besides heart-beating (HB) lung donors to overcome organ shortage. We evaluated the effectiveness of NHB lung transplantation. Methods: The donor and recipient data of all 35 NHB category III lung transplantations (LTx) between January 2005 and December 2009 were reviewed. For comparison, we collected recipient and donor data of a cohort of 77 HB lung transplantations. In both groups, we assessed survival, primary graft dysfunction (PGD), forced expiratory volume in 1 s (FEV1), acute rejection, and bronchiolitis obliterans syndrome (BOS). Results: Thirty-five NHB lung transplantations were performed, five single LTx and 30 bilateral LTx in 12 male and 23 female patients. The donor oxygenation capacity was 61 kPa (interquartile range (IQR), 56–64). Warm ischemia time in the donor was 29 min (IQR, 24–30). Cold ischemic time of the last implanted lung was 458 min (IQR, 392–522). Cardiopulmonary bypass was used 13 times. PGD (1–3) was observed in 45% of the patients at T0, in 42% at T24, in 53% at T48, and in 50% at T72. PGD 3 decreased from 24% at T0 to 6% at T72. The use of nitric oxide (NO) within 24 h after transplantation was necessary in three patients with successful weaning in all. There was no significant difference for donor and recipient characteristics between NHB and HB lung transplantations. Survival, occurrence of PGD, and acute rejection was equal to the HB cohort. The incidence of BOS was lower in the NHB group. The measured FEV1 tended to be better in the NHB group. Conclusion: Lungs from nonheparinized category III NHB donors are well suited for transplantation and can safely increase the donor pool.

Keywords: Lung transplantation; Non-heart-beating donor; Primary graft dysfunction

1. Introduction

The first lung transplantation was performed by James Hardy in 1963 with a graft from a non-heart-beating (NHB) donor [1]. Since the criteria for brain death were introduced and accepted in 1968, transplantation with lungs from heart-beating (HB) donors became the mainstay therapy for patient with end-stage lung disease refractory to medical therapy. Until today, donor organ shortage is the main limiting factor for this treatment. It is estimated that only 15–30% of all HB donors have lungs that are suitable for transplantation [2,3]. This resulted in the reintroduction of the concept of lung transplantation from NHB donors by Egan in 1991 [4]. In 1995, Love et al. performed the first clinical successful lung transplantation with lungs from an NHB donor [5]. The Maastricht classification drawn up in 1995 classifies the NHB donors as uncontrolled or controlled donors [6]. In category I (dead on arrival) and category II (failed resuscitation), cardiac death occurs unexpectedly and the situation for organ recovery is therefore 'uncontrolled'. In category III (withdrawal of life support, awaiting cardiac arrest) and category IV (cardiac arrest in brain-dead donor), circulatory arrest is anticipated and organs can be recovered under 'controlled' circumstances. Steen et al. performed the first transplant from an uncontrolled donor in 2000 after ex vivo evaluation of the lungs [7]. Subsequently de Antonio et al. reported lung transplantation using Maastricht category I and II donors [8]. The experience with the use of controlled donors, mainly Maastricht category III, is growing. This has been reported in recent articles [9–18].

The purpose of this study is to investigate whether the use of lungs from controlled NHB donors category III is a true alternative besides HB lung donors by comparing primary graft dysfunction, development of bronchiolitis obliterans syndrome (BOS), lung function, and survival.
2. Patients and methods

2.1. Study group

Between January 2005 and December 2009, a total of 145 lung transplantations were performed in our center. Among these patients, 35 adults received lungs from category III NHB donors. For this retrospective study, the data of the 35 adult NHB recipients were assessed and compared with an existing cohort of 77 adult HB recipients that were transplanted during the same time period.

2.2. Donor protocol

Heart-beating donors (HBD) and non-heart-beating donors (NHBD) were selected according to the standard International Society for Heart and Lung Transplantation (ISHLT) criteria. When donation is considered, the Dutch National Donor Registry is checked to see whether the patient is registered positive as a donor. Blood group, gender, length, age, medical history, blood gas measurement, and a recent chest X-ray are necessary for a first assessment. If judged suitable, a blood gas at 100% oxygen after at least 10 min of ventilation with 5 cmH2O positive end-expiratory pressure (PEEP) and a bronchoscopy are performed for final assessment of the suitability of the lungs for transplantation. After acceptance of an NHB donor, a time of withdrawal is agreed so that all the transplant teams can be present in the donor hospital in time. The technical procedure of withdrawal is up to the treating physicians and local protocols. No heparin is given before withdrawal of treatment. After circulatory arrest, a 5-min no-touch period was respected. If necessary, the patient was reintubated and a bronchoscopy was performed. Lungs are preserved in our standard way with in situ antegrade flush and a retrograde flush on the back table both with Perfadex. The lungs are gently inflated and stored in Perfadex cooled by surrounding ice. The acceptable time between withdrawal of treatment and occurrence of circulatory arrest was 1 h. The accepted warm ischemia time was 1 h and was defined as the time between circulatory arrest and start of the antegrade flush. Cold ischemic time was defined as the interval between start of the antegrade flush in the donor and the reperfusion of the last implanted lung [14].

2.3. Recipient selection

Recipient selection and donor/recipient matching were performed using international guidelines. All recipients on the waiting list were candidates for both HB lungs and NHB lungs. Lung allocation was based on the waiting time on the waiting list or urgency status according to Eurotransplant allocation rules.

2.4. Primary graft dysfunction

Primary graft dysfunction (PGD) was graded according to the recommendations of the ISHLT considering the PaO2/FIO2 ratio and the findings on chest X-ray. The incidence was compared at different time points (T0 — within 6 h of reperfusion, T24, T48, and T72). PGD was assessed and compared in all lung transplantations and separately in bilateral lung transplantations [19].

2.5. Acute rejection and BOS

Bronchoscopy was performed at discharge from the hospital and thereafter when clinically indicated. Acute rejection was based on histological findings and was graded according to the recommendations of the ISHLT Lung Rejection Study Group [20].

All recipients received induction therapy with basiliximab and triple maintenance immunosuppression with corticosteroids, tacrolimus, and azathioprine or mycophenalate.

BOS was defined as a decrease in forced expiratory volume in 1 s (FEV1) compared to the baseline value and was classified following the recommendations of the ISHLT in BOS grade 0–3 [21].

2.6. Lung function

Lung function assessment was performed at every hospital visit. For this study, we report the FEV1 at 3 months, 6 months, 1 year, and 2 years after transplantation. The FEV1 is expressed as a percentage of the predicted FEV1 of the recipient.

2.7. Variables

Data of 112 patients (35 NHB and 77 HB) were reviewed for donor variables and recipient variables. Age, gender, PaO2 after minimal 10 min of 100% oxygen and a PEEP of 5 cmH2O, days of mechanical ventilation, time until circulatory arrest, cause of brain damage, warm ischemic time, and ischemic time of the last implanted lung were recorded as donor and preservation variables. Recipient variables collected were age, gender, LTx type, use of cardiopulmonary bypass, diagnosis, hospital stay, intensive care unit (ICU) stay, and days of postoperative ventilation.

2.8. Statistical analysis

Data analysis was performed using Graphpad Prism 5 (San Diego, CA, USA). All data are expressed as median (interquartile ranges) unless otherwise defined. Mann–Whitney test, the Fisher’s exact test, and the chi-square test were used to test for significances between both groups. For PGD and BOS, a chi-square test was used to test for a significant difference between both groups at each time point. The Kaplan–Meier method was used to assess the patient survival. A p-value <0.05 was considered significant.

3. Results

3.1. Donors and preservation

Between January 2005 and December 2009, a total of 61 lungs from NHB category III donors were offered to our institution. In six cases the lungs were considered but not accepted because of medical reasons. Logistic reasons, including no transplant capacity (n = 4), no suitable recipient...
(n = 2), and miscellaneous (n = 2) were other reasons to reject the lungs. Forty-seven NHB donor procedures were started resulting in 35 adult NHB lung donations and transplantations and one pediatric lung transplantation. Reasons for not using lungs after the donor procedure was started were absence of cardiac arrest within 1 h (n = 7), emphysematous lung at inspection (n = 2), infection (n = 1), and lung edema after flush (n = 1).

Donor characteristics are listed in Table 1. In the NHB group, circulatory arrest occurred within 17 min (IQR, 10—39 min). The median warm ischemic time was 29 min (IQR, 24—30 min). The cold ischemic time for the last implanted lung was 458 min (IQR, 392—522) in NHB compared to 401 (IQR, 357—88) in HB (p = 0.18). There was no statistical significant difference between NHB an HB.

3.2. Recipient characteristics

Recipient characteristics are shown in Table 2. Thirty-five NHB lung transplantations were performed, five single LTx and 30 bilateral LTx in 12 male and 23 female patients. Three patients underwent a retransplantation for progressive BOS.

3.3. Primary graft dysfunction

PGD (grade 1—3) in the NHB group was observed in 45% of the patients at T0, in 42% at T24, in 53% at T48, and in 50% at T72. PGD grade 3 decreased from 24% at T0 to 6% at T72. There was no significant difference in PGD between both the groups at different time points, although the decrease in PGD 3 was less in the HB group compared to that in the NHB group (from 25% to 11% vs from 24% to 6%) (Fig. 1A).

Time to extubation, stay in the ICU, and hospital stay were comparable in both groups.

3.3. Primary graft dysfunction

PGD (grade 1—3) in the NHB group was observed in 45% of the patients at T0, in 42% at T24, in 53% at T48, and in 50% at T72. PGD grade 3 decreased from 24% at T0 to 6% at T72. There was no significant difference in PGD between both the groups at different time points, although the decrease in PGD 3 was less in the HB group compared to that in the NHB group (from 25% to 11% vs from 24% to 6%) (Fig. 1A). When assessing
and comparing only the bilateral lung transplantsations, NHB lungs had less PGD at T0 and T24 (Fig. 1B).

The use of inhaled NO within 24 h after lung transplantation was necessary in three patients in the NHB group. There were no patients that required postoperative extracorporeal membrane oxygenation (ECMO) support. The use of NO was necessary in three patients in the HB group. One was successfully weaned, one died of PGD, and one was successfully weaned after ECMO.

3.4. Acute rejection and BOS

In the NHB group, two patients (5.7%) developed acute rejection (A2) at 1 month and at 23 months after transplantation. A1 rejection was detected in two patients (2.6%) at 3 months and at 6 months in the HB group. The incidence of BOS was lower in the NHB group compared to that in the HB group (Fig. 2). At 1 year after transplantation, there was no BOS in the NHB group compared to that in the HB group (100% BOS 0 vs 85% BOS 0, \( p = 0.037 \)).

3.5. Lung function

Although there was no significant difference, lung function after transplantation assessed as a percentage of the predicted FEV₁ tended to be better in the NHB group compared to that in the HB group at 3 months, 6 months, 1 year, and 2 years (Table 3).

### Table 3. Transplant function as percentage of predicted forced expiratory volume in 1 s (FEV₁).

<table>
<thead>
<tr>
<th></th>
<th>NHB</th>
<th>HB</th>
<th>( % ) FEV₁</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>32</td>
<td>68</td>
<td>75 (54—90)</td>
<td>0.40</td>
</tr>
<tr>
<td>6 months</td>
<td>32</td>
<td>67</td>
<td>82 (57—97)</td>
<td>0.50</td>
</tr>
<tr>
<td>1 year</td>
<td>26</td>
<td>67</td>
<td>87 (63—101)</td>
<td>0.19</td>
</tr>
<tr>
<td>2 years</td>
<td>15</td>
<td>60</td>
<td>85 (62—112)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

NHB, non-heart-beating; HB, heart-beating. Data are expressed as median (interquartile ranges).

3.6. Survival

Recipient survival is shown in Fig. 3. There was no significant difference between the NHB group and the HB group (\( p = 0.53 \)). Five patients in the NHB group died during follow-up. Graft failure caused by BOS was the reason in one of death in two patients. In the HB group, 22 patients died during follow-up. Two patients died of PGD shortly after transplantation and two patients died due to graft failure.

4. Discussion

To our knowledge, this is the largest single-center study reporting the use of lungs from NHBDs category III. The present study shows that lungs from category III NHB donors perform well compared to lungs from HBs. Importantly there was no difference in survival at 1 year. Furthermore, postoperative ventilation, discharge from ICU, and discharge from the hospital were comparable in both the groups. Finally, in the NHB group there seemed to be less PGD (3—24%), the FEV₁ was higher during follow-up and the incidence of BOS was lower compared to the HB group, although this was not significant.

The NHBD program started in 2004 after the initiation of a renewed national protocol for NHB multiorgan donation by the Dutch Transplant Foundation (NTS). Since then, the number of NHBD has increased from four in 2005 up to 12 in 2009. In 2008 and 2009, 40% and 37.5% respectively of our transplants were performed with NHBDs.

Our results with category III NHB donor lungs are comparable with the results of other NHB programs [9,15—17]. In contrast, the Madrid group [8] with an uncontrolled NHB donor program reported a PGD 3 in 29% of their patients. This higher percentage PGD might be explained by the longer warm ischemic time (118 min) and the acute and less-controlled nature of the uncontrolled NHB donor procedure. Finally, their lung function evaluation is less precise since there are no standard lung function data available in category I and category II NHBDs. Although their reported 1-year and 3-year survival after NHB donation is lower than in our study, this lower survival was not different to their HB results.

The recent annual report of the ISHLT shows that acute rejection is detected in 36% of the patients in the first year after lung transplantation [22]. In our study, 2.8% in the NHB group developed A2 rejection and A1 rejection was detected in 2.6% of the patients in the HB group. This might be explained by tacrolimus-based immunosuppression regimen and by the use of induction therapy with an IL-2R antagonist. However, we only report the histological confirmed acute rejection. Our lower incidence is confirmed by the experience of other transplant groups [10,12,13,16,17].

BOS is present in more than 20% of the patients 2 years after transplantation and is one of the most common causes of death 1 year after transplantation [22]. Our study demonstrates 0% of BOS in the NHB group and 15% of BOS
in the HB group 1 year after transplantation. After 2 years, the incidence between both groups is comparable. We hypothesize that the decrease of inflammatory lung injury before retrieval in the NHBD as shown in animal experiments may be responsible for the lower BOS incidence at 6 months and 1 year after transplantation.

There are differences between category III NHB donation programs. Pretreatment (i.e., heparin or phenolamine) was given before death [10, 12, 13] or after the 5-min interval [17] in other protocols. We only optimized the donor treatment before switch-off but added no treatment [14].

It is difficult to compare our warm ischemia with others. In our protocol warm ischemic time (WIT) was defined as the time between circulatory arrest and start of the anterograde flush which is comparable with the report of De Vleeschauwer et al. [13]. But it is different from the data reported by Snell et al. where WIT was defined as the time between the absence of cardiac output and the start of cold flush preservation [18]. In other reports WIT is defined as part of the interval or the interval between withdrawal of life support and establishing perfusion of the donor lung with cold preservation solution [10, 12] and in some studies WIT is not reported [15, 17].

The most common factor in all reported series is the use of an anterograde flush followed by a retrograde flush through each of the pulmonary veins to remove any pulmonary microthrombi.

We believe that the applied retrograde flush is essential for our good results in the Dutch situation where no heparin is used before withdrawal of treatment. Although the number of NHBDs used is growing, there is still a potential pool of controlled NHBDs (category III) [23] and uncontrolled NHBDs (categories I and II) that is not used. Evaluation of lungs in the uncontrolled donor remains challenging in the absence of arterial blood gases and previous medical history. The Madrid group initially evaluated the lungs using a pulmonary artery flush technique. At the time of organ procurement, 300 ml of donor blood was taken. After an initial flush with Perfadex, the blood was flushed through the pulmonary artery. Subsequently, arterial blood gas analysis, corrected for temperature, was performed on the effluent from the left atrium.

Recently, lungs were assessed using an ex vivo lung perfusion (EVLP) system before implantation [24]. After assessing three lung blocks, two with a ΔPO2 > 400 mmHg were deemed acceptable for transplantation.

The first successful lung transplantation after ex vivo lung perfusion was performed by Steen et al. in 2001 [7]. After 65 min of warm ischemia, 3 h of topical, an ex vivo functional assessment at 37 °C and further 8 h of cold storage successful right lung transplantation was performed. Since then, EVLP is investigated extensively not only as a method to assess donor lungs but also as a tool to preserve and resuscitate donor lungs for a longer period of time [3, 25]. Currently, all the lungs with a donor arrest time longer than 30 min are assessed with EVLP in Toronto [10]. Other groups also have successfully transplanted lungs from controlled NHBDs after EVLP. The use of EVLP looks at the perspective for re-assessment of rejected NHBD donor lungs, for assessment of NHB donor lungs after a prolonged period of warm ischemia or after a period of cardiopulmonary instability during the agonal phase, and for assessment of lungs from uncontrolled NHBDs, leading to the expansion of the NHB donor pool.

The present study suffers from some limitations. First, the study was retrospective and the experience increased with the amount of retrievals and transplantations performed. Second, the patients were not randomly assigned to a specific type of donor. Third, there were more patients with bronchiolitis obliterans in the NHB group compared to that in the HB group. Therefore, the findings need to be confirmed with a prospective study.

In conclusion, this study demonstrates comparable outcome between NHBDs and HBBDs, thereby confirming that lungs from NHBDs may be a safe alternative to increase the donor pool.

References

Appendix A. Conference discussion

Dr S. Clark (Newcastle Upon Tyne, United Kingdom): In common with your experience, we are finding that around 10% to 15% of our transplant activity is from non-heart-beating organ donors. Could you elaborate a little bit on the method that you use for retrieval; in particular, the stand-off time? Also, we have exactly the same experience, with a low incidence of PGD. In terms of the acceptance time, how long do you wait? I understand that you already partially answered that, but we have accepted even up to 2 hours, and if the acceptance time does not drop, then also we will be willing to wait longer to see what’s happening.

Dr Van De Wauwer: We are using about 60 minutes at this moment, unless the patient is very stable and there are no fluctuations in heart rate, no fluctuations in blood pressure, then sometimes we wait longer. Also, when we have the information at 60 minutes that they don’t think it’s going to take long because the blood pressure is dropping and also the heart rate is dropping, then also we will be willing to wait longer to see what’s happening.

Dr L. Hamilton (Newcastle Upon Tyne, United Kingdom): It raises lots of ethical questions as well. One question regarding interventions in the donor before death has occurred — you said you don’t give heparin beforehand, and I understand the reasons for that. What do you think of the concept of giving heparin to improve the quality of the organs?

Dr Van De Wauwer: Yes, indeed it is an ethical discussion and it differs from country to country, but in the Netherlands we agreed not to give heparin, and we didn’t see any problems without the heparin. We had one patient where we saw at the retrograde flush that there were some clots from the flush, but even that patient had no problems. We had one patient where we saw at the retrograde flush that there were some clots from the flush, but even that patient had no problems. We had one patient where we saw at the retrograde flush that there were some clots from the flush, but even that patient had no problems.