A canine experimental study to assess the potential of unilateral double lobar lung transplantation

Keiju Aokage, Hiroshi Date*, Ryujiro Sugimoto, Mikio Okazaki, Daisuke Okutani, Hidetoshi Inokawa, Motoi Aoe, Nobuyoshi Shimizu

Department of Cancer and Thoracic Surgery, Okayama University Graduate School of Medicine and Dentistry, 2-5-1 Shikata Cho, Okayama City 700-8558, Japan

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Abstract

Objective: We recently reported a technique of unilateral double lobar lung transplantation (UDLLT) in a canine model that was associated with satisfactory early pulmonary function. The purpose of the present experimental study was to assess the quality of bronchial healing, complication rates, survival rates and long-term pulmonary function of this new transplantation technique. Methods: Unilateral double lobar lung transplantation was performed in 14 weight-matched pairs of dogs. In recipient animals, two grafts obtained from donor animals were implanted in the right hemithorax after right pneumonectomy. One graft (left graft) was implanted as a right upper lobe in an upside-down position and the other (right graft) was implanted in the natural anatomic position. The immunosuppressed recipients were observed for 3 weeks. Transplanted graft function was assessed under left main pulmonary artery occlusion at 1 and 3 weeks after transplantation. Results: All animals survived the operation. Pulmonary artery kinking (3/14, 21%) and pulmonary venous thrombus (4/14, 29%) were exclusively observed in the graft implanted in the upside-down position. These complications decreased as the number of transplantations increased. Two of the first seven (29%) and five of the last seven recipient dogs (71%) survived for 3 weeks with excellent pulmonary function and good bronchial healing. Conclusions: This procedure was associated with a high complication incidence in the non-anatomically positioned graft. However, a precise surgical technique could decrease these complications. This technically demanding procedure provided excellent pulmonary function and good bronchial healing.

Keywords: Lung transplantation; Living-donor; Recipient

1. Introduction

Since Starnes et al. [1] developed lung transplantation of lobes from two healthy living donors, bilateral living-donor lobar lung transplantation (LDLLT) has become an accepted approach for patients with end-stage pulmonary disease [2,3]. In the existing milieu of cadaveric donor shortage in Japan we began a LDLLT program in 1998 at our institution [4]. Because a limited amount of lung tissue is implanted, this procedure seems to be best suited for children and small adults. In fact, we have turned down a number of patients because of unacceptable size mismatch. Using a canine model, we recently developed a technique of unilateral double lobar lung transplantation (UDLLT) that can be applied to large adult patients [5]. UDLLT was technically possible and associated with satisfactory early pulmonary function. This experimental study was performed to look for a potential clinical technique to treat patients who would be turned down because of size mismatch. The purpose of this study was to assess the quality of bronchial healing, complication rates, survival rates and long-term pulmonary function of this new transplantation technique.

2. Materials and methods

We performed 14 UDLLT in weight-matched pairs of adult mongrel dogs (10.0–26.0 kg). The mean weights of donor and recipient were 14.6 and 14.0 kg, respectively. The left graft (left lower lobe of the donor) was implanted as a right upper lobe in the upside-down position and the right graft (right middle, lower and cardiac lobes of the donor) was implanted in the natural anatomic position (Fig. 1). A detailed description of the technical aspects of UDLLT was reported recently [5]. The following is a summary of the UDLLT procedure.

2.1. Donor operation

Under general anesthesia, the double-lung block was removed after full heparinization without flushing and cooled...
in cold saline solution. The right graft (right middle, lower and cardiac lobes) and the left graft (left lower lobe) were separated from the double-lung block at a back table.

2.2. Recipient operation

Anesthesia was induced with intramuscular ketamine hydrochloride (10 mg/kg) and atropine sulfate (0.01 mg/kg). Intravenous thiopental sodium (2.5 mg/kg) and vecuronium bromide (0.1 mg/kg) were used to facilitate endotracheal intubation. The recipients were placed on a mechanical ventilator and anesthesia was maintained with 0.5% inhalational halothane–oxygen mixture.

A right thoracotomy was performed through the fifth intercostal space, with the animals in the left lateral position. The upper lobe branch of the right pulmonary artery was divided between silk ligatures. The pulmonary artery distal to this branch was divided separately. Pulmonary veins were divided between silk ligatures placed on each venous branch at the hilum. The right upper bronchus and the intermediate bronchus were divided separately. The pericardium was opened around the pulmonary veins to increase the length of recipient left atrium available for subsequent clamp placement. The endotracheal tube was advanced to the left main bronchus for single lung ventilation.

The left graft was placed in the right thorax, after being rotated 180° along the vertical axis and then 180° along the horizontal axis. Thus, in this situation the diaphragmatic aspect of the donor left lower lobe became the apical aspect. The anastomosis between the donor left lower bronchus and the recipient right upper bronchus was constructed using an end-to-end suturing technique with 5-0 Prolene. Then the donor left lower pulmonary artery was anastomosed to the first branch of the recipient right pulmonary artery with 7-0 Prolene. The right graft was then placed in the right chest cavity in the natural anatomic position. The anastomoses of the bronchus and the pulmonary artery were performed by using an end-to-end suturing technique. After placing a vascular clamp as proximal as possible on the recipient left atrium, a suitable cuff for the venous anastomosis was created. The two veins of the donor grafts were approximated side by side with 6-0 Prolene to form one large vein and were attached to the recipient left atrial cuff. Before reperfusion, methylprednisolone (15 mg/kg) was administered intravenously. The two grafts were reperfused and ventilated. The chest was closed after hemostasis was secured and air leaks were controlled. Once awake, animals were immediately extubated. The chest drainage tube was removed about 1 h postoperatively.

2.3. Postoperative management

The dogs received FK506 (0.1 mg/kg) intramuscularly and prednisone (0.15 mg/kg) orally every day [6,7]. For 1 week postoperatively, 500 mg of cefotiam hydrochloride was injected intramuscularly.

2.4. Assessment of pulmonary function and bronchial healing

Function of the transplanted grafts was assessed under occlusion of the left main pulmonary artery at 1 and 3 weeks after transplantation. One week after the operation, surviving animals were reanesthetized and attached to a ventilator. Both lungs were ventilated with a tidal volume of 20 ml/kg, positive end-expiratory pressure of 5 cm H2O, and an inspired oxygen fraction of 1.0, at a rate of 15 breaths per minute. A 5F thermodilution catheter was inserted through the right external jugular vein and positioned in the main pulmonary artery. Hemodynamic changes including pulmonary artery pressure, central venous pressure, and cardiac output using a thermodilution method were measured through this catheter. Femoral artery cannulation with a 23-gauge catheter was used for monitoring systemic blood pressure and arterial blood gases. A left mini-thoracotomy was performed through the fourth intercostal space and the left main pulmonary artery was encircled with a 1-0 silk ligature. Using the silk ligature, the function of the transplanted two grafts was measured after the left pulmonary artery was occluded for 10 min. After the assessment, the occlusion was released and the animal was extubated. At 3 weeks, the same lung function assessment was repeated. Measurements were reported as the mean ± the standard error of the mean. After the 3-week assessment, animals were sacrificed with an overdose of thiopental. Animals were also sacrificed when they could not tolerate the left pulmonary artery occlusion or if the roentgenogram of the chest showed complete opacification of the transplanted grafts.

Bronchial healing was assessed by a fiberscope at each assessment and at autopsy. Bronchial healing was classified in three grades: Grade I, normal healing; Grade II, ischemic ulceration; and Grade III, bronchial dehiscence. Chest roentgenograms were taken immediately after transplantation and after each assessment. Pulmonary angiography was performed before sacrifice.
2.5. Animal care

All dogs received human care in compliance with the European Convention on Animal Care. The study was approved by our institutional ethics committee.

3. Results

The total ischemic time was 258 ± 13 min. All 14 recipient animals survived the operation and were successfully extubated. The results of these 14 consecutive procedures are summarized in Table 1.

Major complications occurred in seven (50%) recipients and these occurred exclusively in the grafts implanted as a right upper lobe in the non-anatomic position. These complications decreased as the number of transplantations increased. Complications occurred in five (71%) of the first seven recipient dogs and in two (29%) of the last seven recipient dogs.

Right upper lobe pulmonary artery kinking was encountered in three (21%) animals. This complication decreased the blood flow to the graft implanted in the non-anatomic position and resulted in bronchial fistula in two animals. By shortening the recipient’s upper bronchus and positioning the donor left graft more carefully, no such complication occurred in the last nine animals.

Pulmonary venous thrombus was observed in four (29%) animals, and caused upper lobe graft congestion (Fig. 2). At autopsy, all the venous thrombi were found near the junction of three suture lines and obstructed the upper pulmonary vein. One animal with a large venous thrombus obstructing the upper and lower pulmonary veins developed a bronchial fistula in the truncus intermedius.

Seven animals (50%) survived for 3 weeks without developing complications. These seven animals tolerated donor left graft more carefully, no such complication occurred in the last nine animals.

PA: pulmonary artery; PVT: pulmonary venous thrombosis; BF: bronchial fistula. Bronchial healing was classified in three grades: Grade I, normal healing; Grade II, ischemic ulceration; and Grade III, bronchial dehiscence.

<table>
<thead>
<tr>
<th>Dog</th>
<th>Survival (day)</th>
<th>Complications</th>
<th>Bronchial healing</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Upper bronchus</td>
</tr>
<tr>
<td>1</td>
<td>28</td>
<td>None</td>
<td>Grade I</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Upper lobe PA kinking, BF</td>
<td>Grade III</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Upper lobe PA kinking</td>
<td>Grade II</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>PVT</td>
<td>Grade I</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Upper lobe PA kinking, BF</td>
<td>Grade III</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>None</td>
<td>Grade I</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>PVT</td>
<td>Grade I</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
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<td>PVT, BF</td>
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</tr>
<tr>
<td>12</td>
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<td>PVT</td>
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<tr>
<td>14</td>
<td>22</td>
<td>None</td>
<td>Grade I</td>
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Table 1
Results of unilateral double lobar lung transplantation

<table>
<thead>
<tr>
<th></th>
<th>One week</th>
<th>Three weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>531.4 ± 72.8</td>
<td>629.2 ± 45.3</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>42.2 ± 6.7</td>
<td>33.6 ± 9.1</td>
</tr>
<tr>
<td>Mean AoP (mmHg)</td>
<td>115.6 ± 13.8</td>
<td>91.9 ± 15.1</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>38.4 ± 5.2</td>
<td>28.9 ± 8.6</td>
</tr>
<tr>
<td>Mean CVP (mmHg)</td>
<td>7.4 ± 1.7</td>
<td>7.7 ± 1.8</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.0 ± 0.8</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>PVR (dyn s cm⁻⁵)</td>
<td>882.2 ± 234.1</td>
<td>744.0 ± 174.2</td>
</tr>
</tbody>
</table>

Table 2
Pulmonary function of seven animals that did not develop complications

Fig. 2. Chest roentgenogram of dog no. 12 on day 10. The left graft implanted in the right upper lobe position was completely opacified due to pulmonary congestion caused by venous thrombosis.
the left pulmonary artery occlusion and showed excellent pulmonary function (Table 2). Good bronchial healing was observed at serial bronchoscopic examination and at autopsy (Fig. 3). Chest roentgenogram showed well-expanded grafts (Fig. 4). Pulmonary angiogram demonstrated no stenosis in the arterial anastomoses (Fig. 5).

4. Discussion

Bilateral LDLLT has developed from an experimental procedure to an accepted therapy as an alternative to cadaveric lung transplantation [1-4]. In this relatively new transplant procedure, two healthy donors donate their right or left lower lobe and these two lobes are implanted to the recipient after bilateral pneumonectomy. Because a limited amount of lung tissue is implanted, this procedure is usually confined to patients of small size. Among 33 recipients receiving bilateral LDLLT in our institution, there were only two adult male patients [4]. A number of patients have been turned down for transplantation because of unacceptable size mismatch.

With the hope of expanding the possibilities for transplantation in large adult patients who are unlikely to survive the long wait for cadaveric lungs, we have developed a novel technique of UDLLT [5]. This new procedure is based on the notion that single lung transplantation has been successfully performed for various noninfectious lung diseases [8,9]. Given the fact that the model has some difference from the human setting, such as chest shape and vascular anatomy, we believe that this model is good enough to develop a technique of UDLLT.

UDLLT is unique and technically demanding for the following reasons: (1) two grafts are implanted in the right hemithorax, (2) the donor left lower lobe is implanted in the upside-down position in the recipient as a right upper lobe, (3) the left lower pulmonary artery of the graft is anastomosed to a smaller artery, the recipient’s right upper pulmonary artery, and (4) two pulmonary veins were...
approximated side by side; therefore, there were two junctions of three suture lines in the left atrial anastomosis.

In spite of several technical points that required elaboration, we reported that UDLLT was technically possible and associated with satisfactory early pulmonary function in a canine experimental model [5]. To assess the potential of UDLLT in the clinical setting, we performed the present chronic animal study. The quality of bronchial healing, complication rates, survival rates and long-term pulmonary function of this new transplantation technique were evaluated.

Right upper lobe pulmonary artery kinking occurred in three of the first five animals. Due to inadequate blood flow to the graft, two animals developed a fatal bronchial fistula in the upper bronchial anastomosis. We speculated that the morphological difference between the upper portion of the recipient thoracic cavity and the donor left lower lobe caused distortion of the arterial anastomosis after the chest was closed. To overcome this problem, the recipient’s upper bronchus and upper pulmonary artery were kept as short as possible. Great care was taken in positioning the left graft in the right chest cavity before starting bronchial anastomosis so as to make the diaphragmatic aspect of the left graft perfectly fit the apical chest wall. By modifying the surgical techniques as mentioned above, right upper lobe pulmonary artery kinking did not occur in the last nine animals.

Pulmonary venous thrombus was observed in four (29%) animals, and resulted in upper lobe graft congestion. It appears important to assure intima-to-intima approximation and to exclude intraluminal muscle. We are not sure if the high incidence of venous thrombus in the present study was due to the side-by-side approximation of the two veins. It is well documented that thrombosis at the atrial suture line is a common complication in a canine lung transplantation model [10,11]. In contrast, this complication is rare in human lung transplantation [12].

We encountered major complications in half of the UDLLT recipients in the chronic animal model. These complications occurred exclusively in the graft implanted in the upside-down position. Couetil et al. [13,14] reported the techniques for lung transplantation in a non-anatomical position. They split the donor left lung and then implanted the left lower lobe in the left hemithorax and the left upper lobe in the right hemithorax [13]. They also reported successful right single lung transplantation using the left lung of a cadaveric donor [14].

Replacing both native lower lobes by two ipsilateral lobar lobes may decrease the risk of anastomotic complication in the graft implanted in the non-anatomical position. However, it may increase the risk of persistent air leakage from interlobar fissure.

Of note was that major complications decreased as the number of transplantations increased in our study. When no complications were encountered, recipient animals survived with excellent pulmonary function and good bronchial healing. Although technically demanding, UDLLT may be a viable new option for large adult patients with end-stage pulmonary disease who are unlikely to survive the long wait for cadaveric lungs.

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References


