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Experimental Study of Mature Pulmonary Lobe Allo-transplantation in Puppies

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Abstract：Background：the use of a reduced-size adult lung transplantation could help solve the profound shortage in pediatric donor lungs. However, the adequate long-term function of mature grafts requires growth in proportion to the recipient's development.

Methods：Six mature left lower lobes from adult beagles (mean weight：12 kg) were harvested and transplanted to 6 immature recipient beagles (age：3 months, mean weight：5 kg) that had undergone a left pneumonectomy (PR). The control group (AR) was 5 adult dogs which had undergone a mature pulmonary lobe allo-transplantation. After transplantation, immnosuppression therapy consisting of cyclosporine A, azathioprine and predonisolone was administered until sacrifice. The right pulmonary artery occlusion test was performed under mechanical ventilation with FiO_2 1.0 at 12 months or later after transplantation. The cardiac output and pulmonary arterial pressure (PAP) were measured, a femoral arterial blood gas analysis (PaO_2 and $PaCO_2$) was performed, and $AaDO_2$ was calculated before and after occlusion at 5, 10, 15, and 30 minutes. The grafts were removed and examined histologically.

Results：In the PR group, 5 dogs survived and 3 dogs tolerated the right pulmonary arterial occlusion test. In the AR group, 3 dogs survived and tolerated the occlusion test. The mean PAP was elevated after opposite side pulmonary artery occlusion. There were no difference in the PaO_2, $PaCO_2$ and $AaDO_2$ levels before and after occlusion test. The PaO_2 levels before and 30 minutes after occlusion were 607±21 and 535±48 Torr in the PR group；560±47 and 563±26 Torr in the AR group, respectively. Histological studies showed a normal architecture of the lung parenchyma but alveolar enlargement was observed in grafts from both the PR and AR groups.

Conclusion：We conclude that in this experimental model of mature lobar transplantation in puppies, the alveolar architecture of a the mature lobe was foumd to show an almost normal appearance, and the long term function of the mature lobe was also found to be well maintained.

Key words：Living donor lung transplantation, Lobar lung transplantation

Introduction

Lung transplantation is a useful therapeutic modality for end stage pulmonary diseases. However, a shortage of donor lungs remains a serious worldwide. Especially for children and small adult recipients, the number of size matching donor lungs is small. As a result, living donor lobar lung transplantation has been performed since 1990[1] instead of brain death donor lung transplantation. In living donor lobar lung transplantation, the outcome is good in the early period after transplantation[2)-7)], but the long term outcome of a graft lobe, including the function and morphological changes, is still unknown.

In the present study, we evaluated the graft function and morphological changes of mature lung lobes which were transplanted to immature recipients.

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Materials and methods

Six adults donor beagle dogs weighting for 10 to 15 kg (mean weight : 12 kg) and 6 recipient beagle puppies weighting 6 to 8 kg (age : 3 months, mean weight : 5 kg) were anesthetized and intubated. A left thoracotomy was performed and then the left caudal lobe of adult dogs were harvested. The recipient puppies underwent a left pneumonectomy. The adult caudal lobes were transplanted in the left pleural cavity of the puppy recipients (PR). In the control group, the adult caudal lobe was allo-transplanted to the adult recipient dogs (AR)which were underwent a left pneumonectomy.

All recipient puppies received immnosuppression therapy consisting of the administration of cyclosporine 20 mg/kg tapered over 3 weeks after surgery to 10 mg, as well as azathioprine 1 mg/kg/day and predonisolone 5 mg/body/day.

Chest X-rays were taken 2 or 3 times weekly during the first one month and 1 or 2 times monthly after transplantation. The bronchoscopical examination protocol was once during the first month after transplantation and every 6 months during the first 2 post-operative years.

The body weight of the puppies was measured once every month until sacrifice.

Pulmonary angiography and the right pulmonary artery occlusion test was performed on the left graft lung at 12 months or later after transplantation. The recipient dogs were anesthetized, intubated and put in a supine position. A balloon catheter was inserted through the right femoral vein and placed in the right main pulmonary artery. A Swan-Ganz catheter was inserted through the left femoral vein to the truncus pulmonary artery. The right pulmonary artery was occluded by a balloon catheter. Mechanical ventilation with FiO_2 1.0, tidal volume 30 ml/kg and 16 cycles/minute was performed. The cardiac output and pulmonary arterial pressure (PAP) were measured, a femoral arterial blood gas analysis (PaO_2 and $PaCO_2$) was performed, and $AaDO_2$ was calculated before and after occlusion at 5, 10, 15, and 30 minutes.

After the pulmonary artery occlusion test, the graft was removed and stained with hematoxylin-eosin in order to undergo a histological examination.

Results

In the PR group, 1 dog died of acute rejection 2 weeks after transplantation and 5 dogs survived 12 months or more. Three dogs tolerated the right pulmonary arterial occlusion test. In the AR group, 3 dogs survived and tolerated the occlusion test. One dog died of acute rejection 16 days after transplantation, and 1 dog died due to pulmonary vein thrombosis on day 5 after surgery.

The results of the right pulmonary artery occlusion test are shown in Table 1. The cardiac output increased in the PR group, and it did not change in the AR group after pulmonary artery occlusion (Figure 1). The mean PAP was elevated from 16.7

Table 1. Right pulmonary artery occlusion test

		CO	mPAP	PaO_2	$PaCO_2$	$AaDO_2$
Mature lobar lung allograft to puppies						
pre-occlusion		2.6±1.2	16.7±6.7	607±21	21.8±8.1	80±26
Post-occlusion	5 min	3.5±1.6	25.0±8.7	400±239	41.8±5.1	263±143
	10 min	3.4±0.8	22.3±9.3	506±95	45.0±3.5	143±102
	15 min	3.9±1.6	21.3±7.8	524±57	41.2±9.3	142±49
	30 min	3.5±1.1	20.3±8.4	535±48	39.9±10.3	130±49
Mature lobar lung autograft to adult dogs						
Pre-occlusion		4.0±1.1	20.0±10.0	560±47	20.5±10.8	113±32
Post-occlusion	5 min	4.1±1.4	34.0±13.9	583±52	23.4±10.9	136±58
	10 min	4.4±1.8	33.3±14.4	554±67	26.8±12.0	127±64
	15 min	4.0±1.5	32.3±15.3	550±46	26.1±11.4	132±47
	30 min	4.2±1.8	32.3±15.3	563±26	27.1±10.1	118±24

CO : cardiac output, mPAP : mean pulmopnary arterial pressure

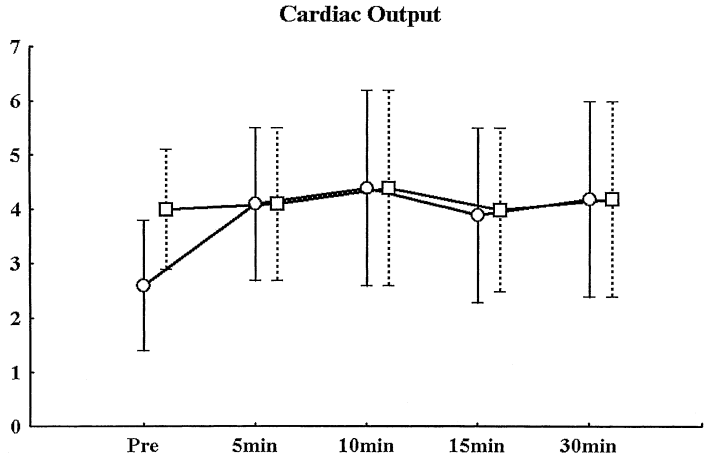

Figure 1. Cardiac output of grafts before and after right pulmonary artery occlusion ; The circle represents the PR group and the square represents the AR group.

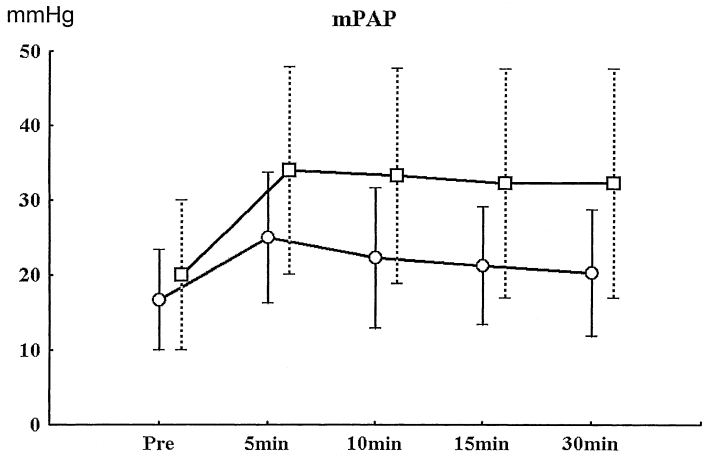

Figure 2. The mean pulmonary artery pressure before and after right main pulmonary artery occlusion ; The circle represents the PR group and the square represents the AR group.

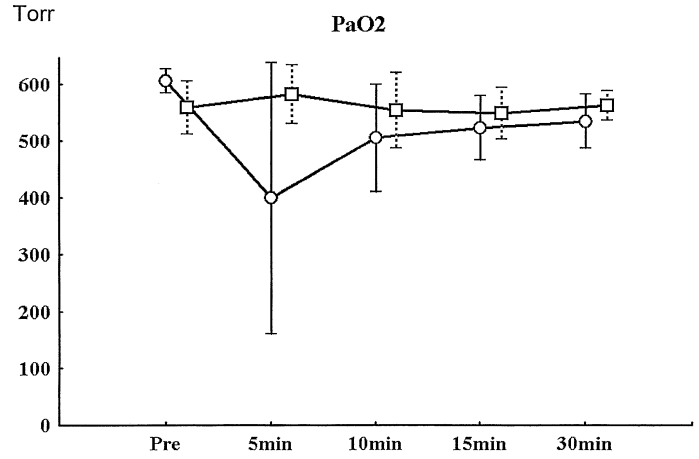

Figure 3. The PaO_2 level before and after the right main pulmonary artery occlusion ; The circle represents the PR group and the square represents the AR group.

±6.7 to 21.3±7.8 mmHg at 15 minutes after the occlusion in the PR group, and from 20.0±10.0 to 32.3 ±15.3 mmHg in the AR group (Figure 2). The mean PAP after occlusion tended to increase more in the AR group more than in the PR group, but there was no significant difference in the mean PAP elevation between both groups. No differences wereseen in the PaO_2, $PaCO_2$ and $AaDO_2$ before or after occlusion test(Table 1). The PaO_2 before and at 30 minutes after occlusion was 607±21 and 535±48 Torr in the PR group ; 560±47 and 563 ±26 Torr in the AR group, respectively (Figure 3). The $PaCO_2$ was 21.8±8.1 and 39.9±10.3 Torr in the PR group ; 20.5±10.8 and 27.1±10.1 Torr in the AR group (Figure 4). The $AaDO_2$ was 80±26 and 130±49 Torr in the PR group ; 113±32 and 118 ±24 Torr in the AR group (Figure 5). The mean value of the $PaCO_2$ in the PR group tended to be higher than that in the AR group.

Histological studies showed a normal architecture of lung parenchyma but alveolar enlargement was observed in the grafts of both the PR and AR groups (Figure 6A, B). Obliterative bronchiolitis (OB) was not observed in the grafts of both the PR and AR groups.

Discussion

Since Starnes[2] reported 2 clinical living-related lobe transplants and 1 cadaver donor lobe trans-

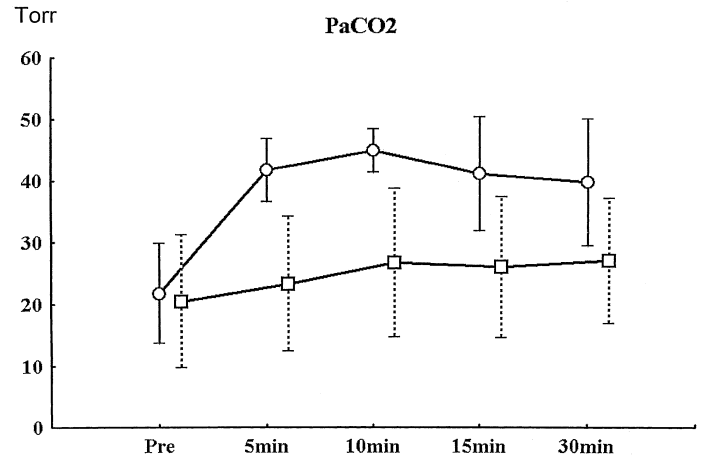

Figure 4. The $PaCO_2$ level before and after the right main pulmonary artery occlusion ; The circle represents the PR group and the square represents the AR group.

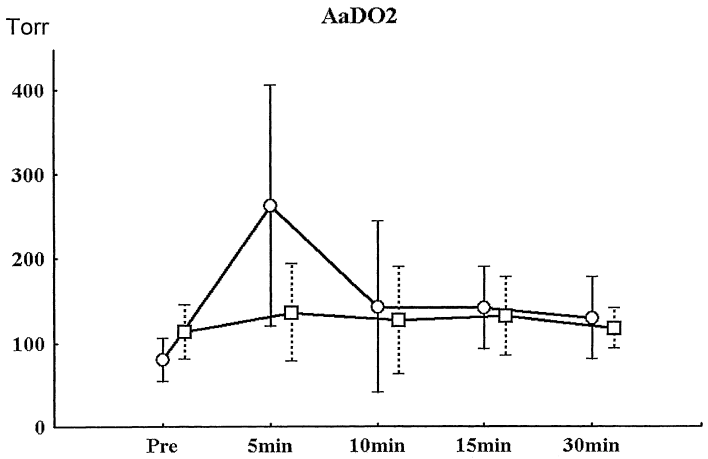

Figure 5. The $AaDO_2$ level before and after the right main pulmonary artery occlusion ; The circle represents the PR group and the square represents the AR group.

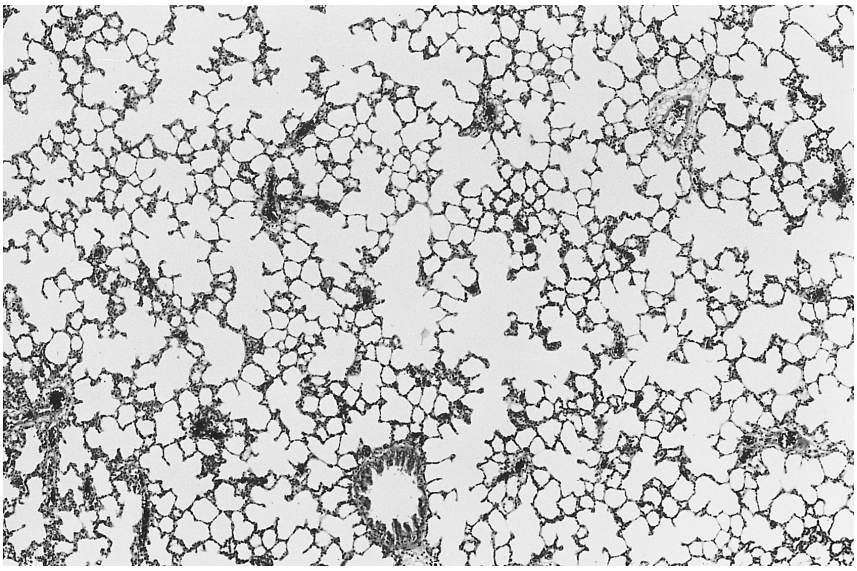

Figure 6A. A microphotograph of the grafts of the PR group.

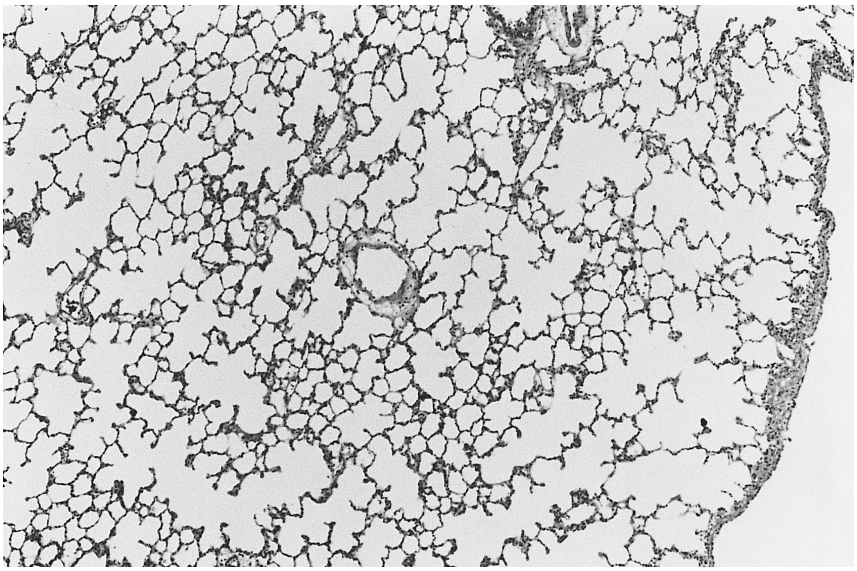

Figure 6B. A microphotograph of the grafts of the AR group.

plant in children, living–related and cadaver lobe transplantation have been expected to increase as a treatment option for selected children and small adults with end–stage lung disease. In many institute in the world, including in Japan, either single or double living donor lung lobe transplantation has been performed.[1)–7)] Careful donor evaluation, skilled intraoperative management and surgical techniques, and diligent immediate postoperative care and follow–up all contribute to better outcomes in such cases. However, the long term outcome of grafts is still unknown.

In experimental studies, the volume and weight of the graft lung lobe has increased.[8)9)] Kern[8)] reported that no significant differences were seen in the functional residual capacity or morphologic analysis of total alveolar number and alveoral size between the transplanted and nontransplanted mature left lower porcine lung 12 weeks after transplantation into growing piglets. Hislop[10)] reported, in experimental study of adult rodent lung lobe transplant to juvenile rats, that an adult lobe

is still viable and has a normal architecture after 6 months.

On the other hand, Duebener[11] reported that questions remain regarding whether mature lung grafts can guarantee sufficient long–term gas exchange in growing recipients. Because mature pulmonary lobe grafts tend to fill up the growing left hemithorax, and emphysema–like structure of the grafts were observed without any evidence of alveolar growth in the mature lobar transplants.

In our experimental model of mature lobar transplantation in puppies, the alveolar architecture of the graft lobe is an appearance of emphysema, although normal respiratory function was observed at 12 months after transplantation. An elevation of the mean PAP in the PR group after right pulmonary artery occlusion tended to be greater than that in the AR group. In adult dog recipients, lung grafts tended to expand rapidly after transplantation. However, in puppy recipients the lung grafts expanded gradually as the recipients grew. These findings suggest that a rapid expansion of a graft lobe has results in a decrease in the pulmonary vessel elasticity while also causing irreversible morphological changes in the pulmonary vasculature.

Woo[6] reported the incidence of obliterative bronchiolitis in living donor lobar lung transplant patients to be lower than in cadaveric whole lung transplant patients. Obliterative bronchiolitis was not found to be the chief cause of mortality in pediatric living donor recipients. In our experimental study, obliterative bronchiolitis was not observed in mature grafts at 12 months or later after transplantation.

It is necessary to continue to investigate the long–term morphological and functional changes of mature lung lobe transplated immature recipients.

Conclusion

We conclude that in this experimental model of mature lobar transplantation in puppies, the alveolar architecture of a mature lobe showed almost normal appearance, and the long term function of a mature lobe was well maintained. The outlook for comparable transplants in children is therefore promising, although, the clinical situation for humans way can be complicated by rejection, infection and the selected treatment strategies

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