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Experimental study on lung preservation-function of a 6 hour-preserved donor lung.

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ABSTRACT : A donor lung was preserve during 6 hours by means of simple immersion with 4℃ modifield Euro-Collin's Solution and it was orthotopically transplanted. The function of transplanted lung was evaluated in terms of O_2 intake by gas exchange and hemodynamic study following transplantation.

The results were as follows 1) PaO_2 values were significantly fallen immediately after transplantation. However, these were reverted to the normal on day 7. 2) Intrapulmonary shunt rates did not significantly vary. In contrast, A-aDO_2 values correlated with PaO_2 values, reflecting uneveness of ventilation/perfusion and failure of diffusion in the early stage of postoperation. 3) Hemodynamically the mean pulmonary artery pressure and the pulmonary vascular resistance were increased immediately after transplantation but these returned on day 14. 4) On chest x-ray film, the infiltrative shadow on the transplanted lung was gradually reduced on day 7 and on day 14, the transplanted lung had become normal aeration on chest x-ray film. 5) In the early stage of postoperation, main histologic finding of a storaged donor lung was interstitial lung edema.

In conclusion, it is clinically applicable that a 6 hour storaged lung by simple immersion with modified Euro-Collin's solution is well functioning and its function should be expected to be the same as that of nonstoraged one.

INTRODUCTION

The surgical outcome of organ transplantation has become remarkably improved since cyclosporin A developed. In contrast, the result of lung transplantation was poor until long term survivor had been obtained by Toronto group in 1983. There are many problems to solve in order to achieve clinical application of lung transplantation, such as difficulty of donor lung preservation, early detection of immunologic rejection, pathogenesis of lung edema induced in early stage of lung transplantation.

It, therfore, is a most improtant that function and hemodynamics of a donor lung is accurately evaluated and it is applies for postoperative care of lung transplantation to improve the surgical outcome. In recent year, various traffic network has developed. Thereby it is enough time duration of 4 to 6 hours to procur a donor lung from distant sites all over the Japan, if necessary.

The aim of this study is to clarify the function and hemodynamics of a donor lung immediately after transplantation by means of the simple preservation of immerse and also to make clear the possibility of clinical application.

MATERIAL AND METHOD

Twenty-five mongrel dogs were anesthetized with intravenously given 25mg/kg of pentobarbital, intubated and ventilated with using Havard ventilator (60% 02 in inhalated gas, 25ml/kg of tidal volume, 14 of respiratory rate). Left thoracotomy was made at the 5th ICS, thereafter all dogs were heparinized with 5000 u heparine. The left lung was removed.

All the dogs were divided into the two groups.

Group I : immediate left allolung transplantation. Fifteen dogs (11.3kg of average body weight) received orthotopic allolung transplantation according to Veith'method 2).

Group II : a 6 hour preserved allolung transplantation, the left lungs from ten dogs (10kg of average body weight) were removed and immersed into 4 ℃ modified Euro-Collins solution whose composition was shown in Table 1 for 6 hours. Therefore it was orthotopically transplanted. The steps of lung transplantation were anastomosed in the order of left atrial cuff, pulmonaray artery and bronchus, in the former two 5-0 prolene and in the latter 4-0 prolene were used for anastomosis.

Table 1. The Composition of modified Euro Collins solution

K_2HPO_4	7.4	g/ℓ
KH_2PO_4	2.05	
KCl	1.12	
$NaHCO_3$	0.84	
Glucose	35	
Electrolytes		
Na^+	10	mEq/ℓ
Ka^+	115	
Cl^-	15	
HCO_3^-	10	
HPO_4^{2-}	85	
$H_2PO_4^-$	15	

The function and hemodynamics were assessed by the following method.

Unilateral pulmonary artery occlusion test (UPAO-test). A 7F-directred thermodilution catheter was introduced to the right pulmonary artery under direct vision by fluoroscopy and a 5F-catheter also was anchored to the left pulmonary artery to measure the pressure and to take the sample of mixed venous blood as shown in Fig. 1.

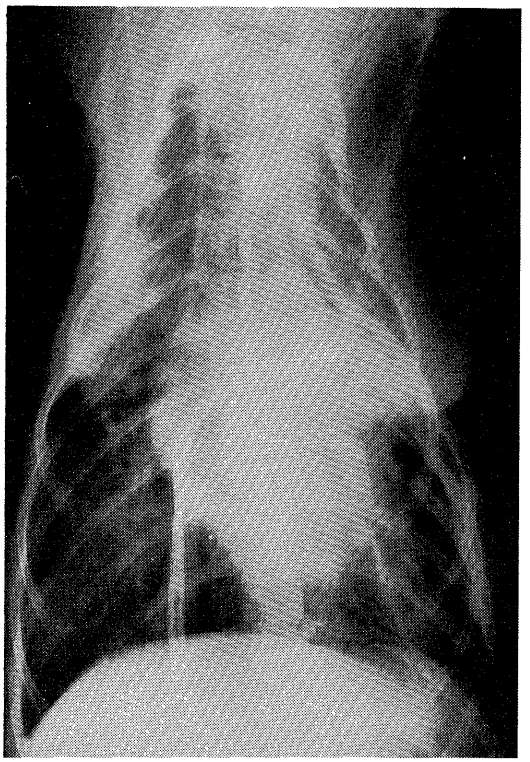

Fig. 1. The method of UPAO-test. A 7 F-thermodilution catheter is placed in the right pulmonary artery and a 5 F catheter placed in the left pulmonary artery.

After the study state of hemodynamics was confirmed for 20 min on the condition of inhalation of 100% O_2, unilateral pulmonary artery was occluded for 10 min and systemic pressure, cardic output, PaO_2 and $PaCO_2$ in peripheral a rterial and PvO_2 and $PvCO_2$ mixed venous blood and cardia output were measured before and after a 10 min. UPAO-test.

The pressures were measured by using polygraph RMP 6004S (Nihonkoden Co) and cardiac output was calculated by thermodilution meter MTC-6100 (Nihonkoden Co). The calculation was as follows :

Intrapulmonaray shunt rate : Qs/Qt=CeO2/CeO2-CvO2
A-aDo2 : PAO2-PaO2 = PIO2-PaCO2/R-PaO2 (R : gas exchange rate 0.8)
Pulmonary vascular resistence (PVR)
PVR=mPAP-LPAWP/CO-80 dyne sec/cm-5
UPAO-test was repeated immediately after, on day 7, on day 14 respectively. In group II, UPAO-test was made on day 3. Histologic examination of a transplanted lung were performed on day 3, 7 at sacrifice to compare with the degree of lung edema, pneumonia and immunologic rejection. These dogs were prescribed 20mg/kg/day of cyclosporin A with 1g of AB-PC and chest xp examination was taken on day 1, 3, 5, 7 and thereafter twice a week.

Operative deaths and feasibility of UPAO-test were analyzed with X2-test and other statistical analysis was made by Wilcoxon-test. The data were expresssed with mean values ± SD.

The dogs subjected to this study were supplied by Animal Center in Nagasaki University School of Medicine and fed, and sacrified according to the rule provided by the Animal Center.

RESULTS

1. Survival following allolung transplantation and achievement of UPAO-test (Table 2, 3)

The operative deaths within 7 days were 3 in Group (20% of death 3/15) and 3 in Group II (30% of death. 3/0) respectively without significant difference in both groups. Achievement of UPAO-test in Group I was 53.3% (8/15) immediately after, 72.7% (8/11) on day 7. 87.5% (7/8) on day 14 respectively. In contrarst, it in Group II was 70% (7/10) immediately after, 66.7% (4/6) on day 3.75% (6/8) on day 7 85.7% (6/7) on day 14.

In both groups, there was a tendency that it was more easy to perform UPAO-test with elapsing time after transplantation and there was no statistically significant difference in the results of UPAO-test in both groups.

Table 2. mortality rate in lung graft of canine

	Non preserved group	6 hrs preserved group
graft	15	10
death ※	3	3
mortality rate (%)	20	30

※ death within 7 days

Table 3. Tolerance rate of UPAO-Test

Days post operatively	Non preserved group	6 hrs preserved group
0 POD	53.3% (8/15)	70.0% (7/10)
3 POD		66.7 (4/ 6)
7 POD	72.7 (8/11)	75.0 (6/ 8)
14 POD	87.5 (7/ 8)	85.7 (6/ 7)

2. PaO_2 (Fig. 2)

In group I PaO_2 values showed 92.7 ±46.0 mmHg immediately after, 231.7±115.4 on day 7, 259.1±51.3 on day 14 when compared with 281 ±97.0mmHg of preoperative value as the control. PaO_2 values immediately after transplantation fell down as compared with a control ($p<0.01$).On the contrary, the values on day 7 and 14 increased ($p<0.05$ $d<0.01$) with no significant difference as compared with a control.

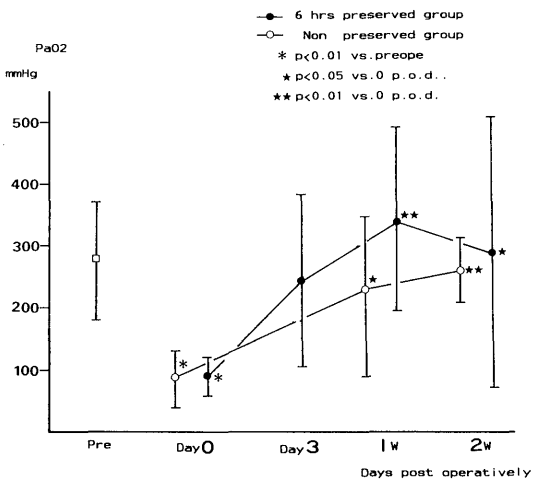

Fig. 2. Changes in mean PaO_2 after transplantation

In group II, PaO_2 values indicated 91.2±29.2 mmHg immediately after, 245.4±136.9 on day 3, 340.9±151.2 on day 7 290.5±216.8 on day 14. PaO_2 values immediately after transplanta-

tion fell down as compared with prior to transplantation, thereafter on day 7 and 14, these significantly increased ($p<0.01$ $d<0.05$) without significant difference as compared with a control. And also there was no significant difference between time-course changes in PaO_2 in both groups.

3. $PaCO_2$ (Fig. 3)

In Group I, $PaCO_2$ values were 36.4 ±10.6 mmHg immediately after, 25.2 ±52 on day 7, 15.5±6.9 on day 14 as compared with 32.7+6.5 mmHg prior to transplantation. There was no increase in $PaCO_2$ during the postoperative period. On the other hand, in Group II, these were 41.4 ±12.2mmHg immediately after, 41.0 ±9.2 on day 3, 34.4±9.1 on day 7. 41.6±9.4 on day 14 respectively without any remarkable changes.

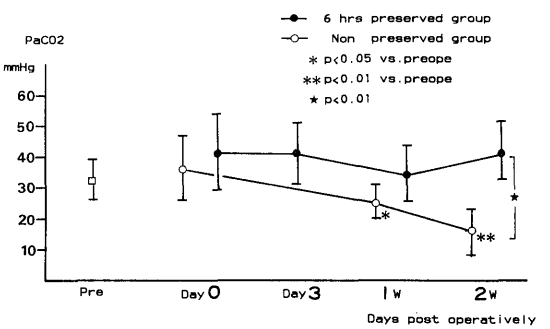

Fig. 3. Changes in mean PaCO2 after transplantation

4. Intrapulmonary shunt (Fig. 4)

In group I, the rates of intrappulmonary shunt were 21.3±4.7% immediately after, 28.1 ±15.1 on day 7, 24.4±12.0 on day 14. Without any significant fluctuation as compared with 27.8 ±5.3 % prior to transplantation. In group II, these were 27.6±6.3% immediately after, 26.5±7.2 on day 3, 23.3±11.7 on day 7, 21.8± 16.7 on day 14. There was no statistically significant difference between the two groups, and before and after transplantations.

5. A-aDO2 (Fig. 5)

In group I, A-aDO2 values were 582.9 ±58.0 mmHg, 452.3±116mmHg on day 7, 432.5±53.7 on day 14 as compared with 408.0±81.8mmHg. There were significantly high when compared

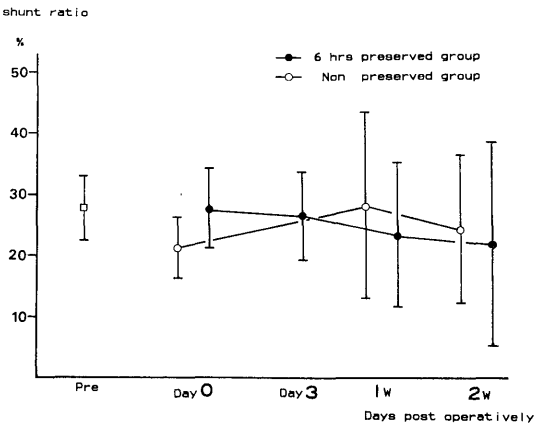

Fig. 4. Changes in mean intrapulmonary shunt ratio after transplantation

with the control prior to transplantation ($p<0.01$) and also with elapsing time these were gradually increased on day 7 d 14 ($p<0.05$, $p<0.01$).

In Group II, A-aDO2 values were 587.4 ±43.2 mmHg immediately after, 441.2±139.4 on day 3. 343.7±140.1 on day 7 392.0+198.4 on day 14 respectively. These were increased immediately after transplantation, thereafter gradually decreased ($p<0.01$, $p<0.05$). However, there was no statistical difference between the values prior to and after transplantations and between the two groups.

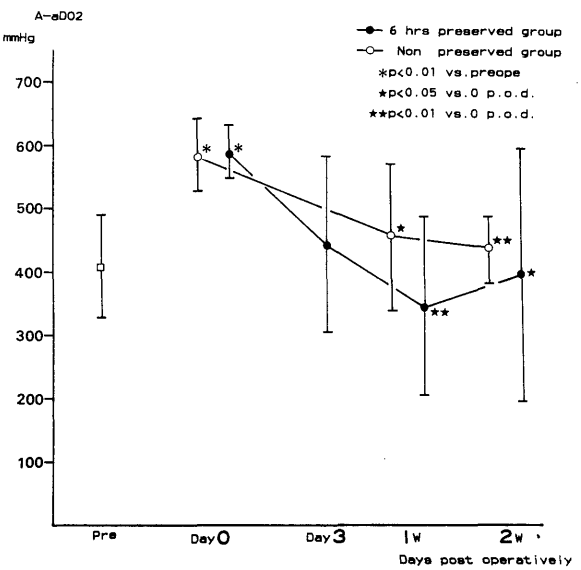

Fig. 5. Changes in mean A-aDO2 after transplantation

6. Mean pulmonary artery pressure (PAP) (Fig. 6)

In Group I, PAP values were 31.6+5.9 immediately after transplantation, 28.1 +1.05 on day 7, 23.6+4.2 on day 14 with significant increase ($p<0.05$) as compared with the control of 20.6 +3.1mmHg, and decreased on day 14 ($P<0.05$). In Group II, these were 35.6 +9.6 on day 0, 32.5+11.0 on day 3, 25.3+8.6 on day 7, 22.5+5.8 on day 14 respectively. The value immediately after transplantation was significantly higher than that prior to transplantation ($p<0.01$), thereafter it was gradually decreased with significant difference ($p<0.05$) as compared with the control.

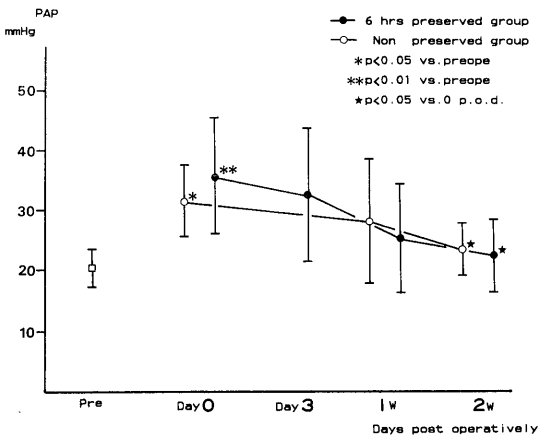

Fig. 6. Changes in mean pulmonary arteial pressure after transplantation

7. Cardiac output (Co) (Fig. 7)

In Goup I, CO values were 1.10+0.241/min on day 0, 1.80+0.62 on day 7, 1.76+0.56 on day 14 without any significant difference. On the other hand, in Group II, CO values showed 0.93 +0.341/min on day 0, 1.35+0.46 on day 3, 1.55+0.32 on day 7, 1.48+0.57 on day 14 with significant reduction ($p<0.05$), a maximum reduction was on day 7 ($p<0.05$). There was no significant difference between the two groups.

8. Pulmonary vascular resistence (PVR) (Fig. 8)

In Group I, PVR values were 2194.4+611.3 dyne. sec/cm-5 immediately after, 1030.8+895.6 on day 7, 595.3+206.9 on day 14 with significant increase ($p<0.01$) as compared with the

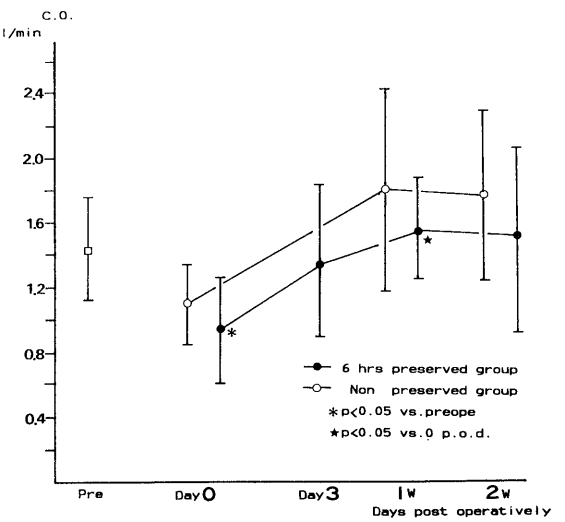

Fig. 7. Changes in mean cardiac output after transplantation

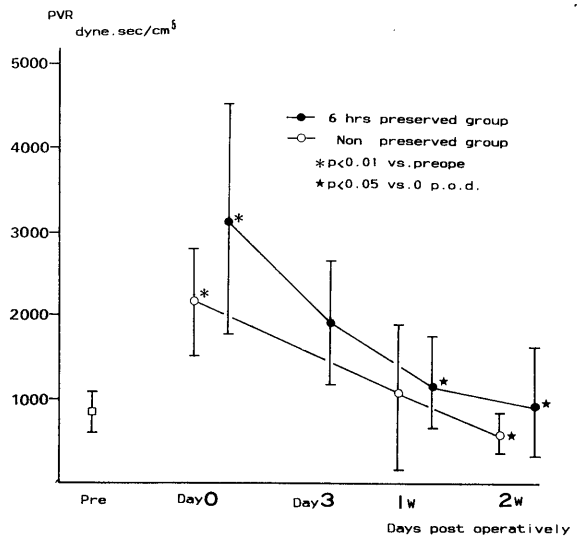

Fig. 8. Changes in mean pulmonary vascular resistance after transplantation

control of 839.0±234. dyne. sec/cm-5. However, these were gradually decreased ($p<0.05$) without significant difference as compared with the control. In Group II, PVR values were 3161.1±1389.3 dyne. sec. cm-5 immediately after, 1910.7±743 on day 3. 118.2±562.5 on day 7 966.5±649.4 on day 14 respectively. The value immediately after transplantation was significantly more increased than that prior to transplantation, thereafter PVR reduced on

Table 4. The findings on chest roentgenography

Days post opectively	findings on chest Xray	n
1 ~ 5 POD	an alveolar infiltration shadow poor aeration	7
7 POD	reduced alveolar infiltration shadow, improved aeration	6
	increased infiltration shadow	1
14 POD	clearing of infiltration shadow and complete dissolution of all abnormalities	6
	increased infiltration	1

day 7 and 14 with significant difference ($p < 0.05$) and these became no difference as compared with the normal with time.

9. Chest X--ray film findings (Table 4)

Chest X-ray films were sequentially taken for 2 weeks. The infiltrative shadow was increased during the 3rd to 5th day duration in 7 out of 10 dogs, thereafter it decreased on day 7 and disappeared on day 14 with an excellent aeration. (Fig. 9, 10 and 11). One of them had an increased infiltrative shadow on day 7 but it converted to well aerated shadow on day 14. The other one had a remarkable shadow of infiltration without aeration on day 14. Histologic examination revealed the finding of diffuse perivascular cuffing by monocyte which was compatible with immunologic rejection.

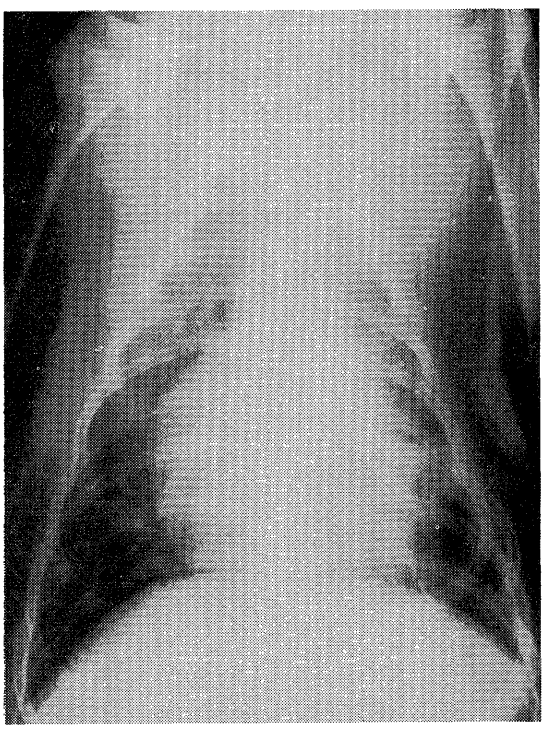

Fig. 9. Plain chest roentgram of a dog 3 days after transplantation reveals that the density of the left lung is increased in the upper and the middle lung fields.

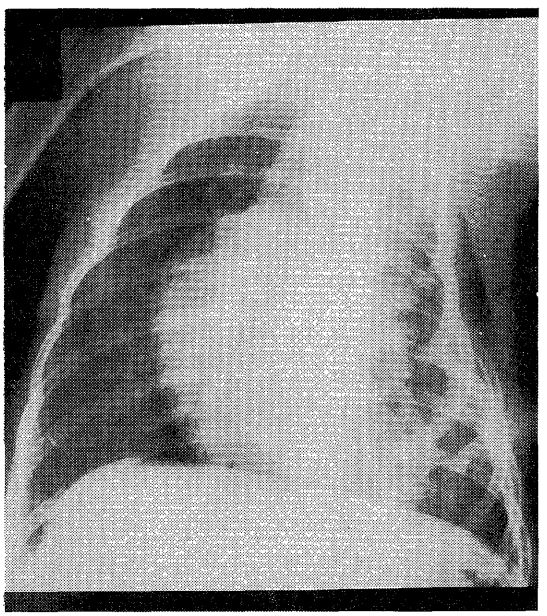

Fig. 10. Plain chest roentgenogram of a dog 7 days after transplantation reveals that the density of the left upper lung field is decreased and its aerated surface area is increased.

10. Alteration of histologic finding on transplanted lung.

In Group I, immunologic rejection was seen

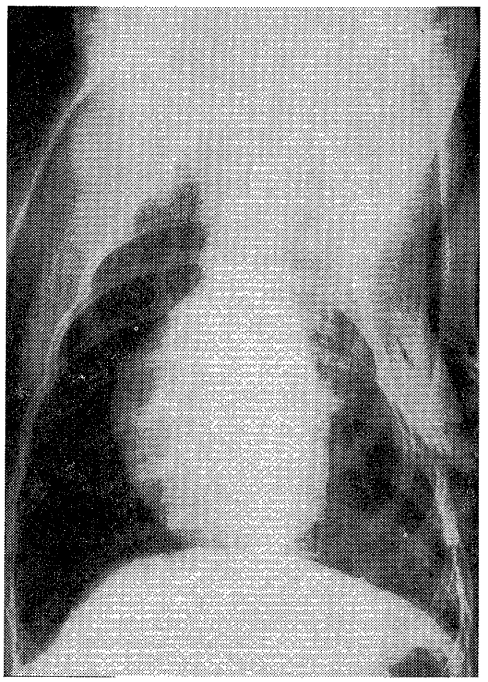

Fig. 11. Plain chest roentgenogram of a dog 14 days after transplantation reveals that the transplanted lung has become largely normal

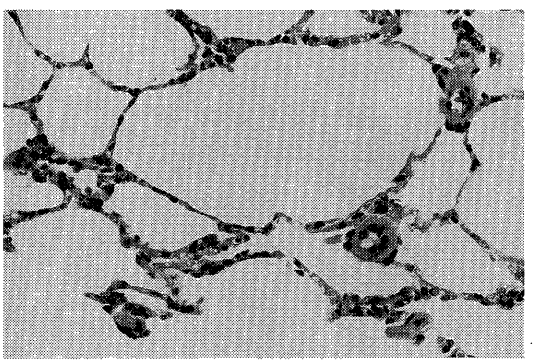

Fig. 12. Photomicrograph of a section from the preserved lung graft before transplantation showing normal morphology (H & E ×100)

in one out of 7 dogs on day 14. In contrast, donor lung immediately after transplantation kept maintaining almost normal histologic pattern. However, histologic examination in donor lungs taken by open lung biopsy from the 2 dogs revealed slight degree of congestion and interstitial edema on day 3 (Fig. 13). In

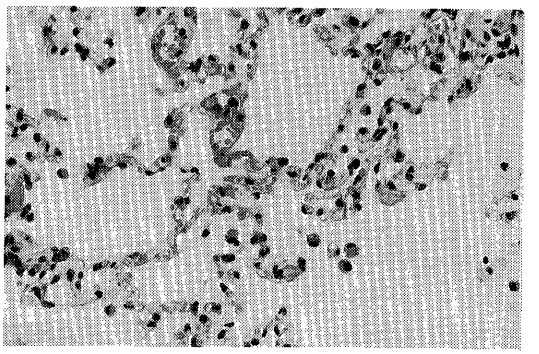

Fig. 13. Photomicrography of a section of open lung biopsy done on day 3 after transplantation showing mild interstitia 1 congestion and edema (H & E ×100)

contrast, on day 14, 5 dogs out of 6 showed immunologic rejection. And 4 perivascular cuffing, one peribronchial cuffing, 2 interstitial edema, 1 alveolar edema. One was a finding of healthy lung without immunologic rejection.

DISCUSSION

Since Juvenelle[3] succeed in experimental lung autotransplantation in dog, much research work has been achieved. On the other hand, since Hardy[4] reported a successfully clinical case, fifty or more cases have been made until recently. However in accordance with developing cyclosporin A, organ transplantation was far advanced[5]. Cooper[1] obtained a 5 year and more survivor but the surgical outcome of lung allotransplantation was not satisfied as compared with those of kidney, heart and liver transplantations.

The reasons for poor outcome of lung allotransplantation are that preservation of a donor lung is not established, adequate suppression and monitoring methods for immunologic rejection are not detected, the problem about specific phenomenon of reimplantation response to lung allotransplantation is not solved yet.

As the methods of donor lung preservation, various means such as simple cooling, continuous perfusion, hyperbaric presevatrion, cadavor perfusion have been evaluated. As for the composition of storage solution and the

intratracheal pressure, ideal storage condition has been studied. Handa[6] recommended the composition similar to extracellular fluid and Hoyer[7] reported a successful long survivor by using storage solution in which the composition was almost the same with intracellular fluid. However which composition of storage solution is ideal or not is an unsettled problem.

On the other hand, as to the condition of intratracheal pressure, Veith[8] reported that the maneuvor of inflation and continuous ventilation of a donor lung enables preservation time to elongate.

In this study, the method of a 6 hour storage by simple immersion with 4 ℃ modified Euro-Collins sollution. As a rule, respiratory function and hemodynamics of a storaged donor lung were experimentally assessed by means of contralateral pneumonectomy test[9], contralateral pulmonary artery ligation[10], lung perfusion scintigram[11] contralateral pulmonary artery occlusion test by balloon catheter[12] simulatenously bilateral lung transplantation[13], contralateral bronchial occlusion test by double lumen tube[14]. It is no doubt that an ideal model of experiments is simulatenous bilateral lung transplantation. However, it is great surgical insult for a recipient and complete denervation as cited by Patterson[15] by which respiratory cycle may be altered enough not to survive for a long time because of great surgical insult and edematous change in a donor lung in acute stage of transplantation.

It is not adequate for quantitative evaluation of donor lung function by means of perfusion scintigram. The one drawback of contralateral bronchial occlusion test is generation of significant increase in intrapulmonary shunt. Therefore, in early stage of lung allotransplantation contralateral pulmonary artery occlusion test by balloon catheter is of great use to evaluate the transplanted lung function.

PaO2 in a 6 hour storage lung fell significantly down rather than that in immediate transplanted lung. Thereafter it was gradually recovered on day 7 and there was no difference in PaO_2 between storaged and nvn-storaged transplantation lungs. Prop[16] regarded edematous lung immediatly after transplantation as reimplantation response. It is accepted on the basis of denervation of hilar stripping, interruption of lymphatic channels, ischemic damage to a donor lung[17]. Stiegelman[17] clarified that reimplantation response was enhanced on day 3 and it was lessened on day 14. Kawahara explained that reimplantation response is improved on day 7 and returned to normal on day 4. In this study, even in a 6 hour storaged donor lung, infiltrative shadow on chest x-ray film was increased on day 3 and then significantly reduced on day 7. PaO_2 was recoverd on day 7. There was no singificnat changes in intrapulmonary shunt. On the other hand, changes in A-aDO_2 values correlated with that in PaO_2.

The causes of decreased PaO_2 are hypoventilation, impaired diffusion, ventilation/perfusion uneveness, increased intrapulmonary shunt. It is well known that $PaCO_2$ value is a most important indicator to express the function of alveolar ventilation[18]. The results of this study have denied the fact that hypofunction of transplanted lung is based on hypoalveolar ventilation and increased intrapulmonary shunt. Main causes of hypofunction of transplanted lung immediately after transplantation is due to impaired diffusion and ventilation/perfusion uneveness because of consistent A-aDO_2 and PaO_2 values despite alveolar-capillary block.

Veith[14] also pointed out that the appearing time of reimpantation response is consistent with appearance of decrease pulmonary compliance and decreased ventilation/perfusion uneveness. Tsuji[20] insisted on vasospasm of transplanted lung and Baranski[21] also clarified that denervation caused spasm of the pulmonary artery vasculature. Regarding regeneration of interrupted lymphatic channels. Tomita[22] reported that regeneration began across the anastomotic line of the bronchus and also Tsuji[20] emphasized that lymph accumulation did not longer cause lung edema with elapsing two weeks.

In this study it is considered that interruption of lymphatic channels is one of the main etiologic factors causing edematous change of the transplanted lung.

In recent year, the study focuses damage to

a donor lung on superoxide activity and it causes damage to cell membran and to vessel permeability[23]. Date[24] reported that damage to vessel permeability was able to be prevented by administering SOD. Breda[25] pointed out that exclusion of leucocytes made it possible to reduce

From these results. it is considered that effectively unknown pathogenesis of implantation response is clarified and effectively preventive means may be valid.

Based on a result of hemodynamic, study, increased pulmonary artery pressure was noted in spite of decreased CO and no change in the pulmonary artery wedge pressure. It is due to damage to the vascular beds of the pulmonary artery in a donor lung. The reason for increased PVR are denervation, anastomotic stenosis of pulmonary artery, and damage to vascular beds by hypoxia and so on. Fujimura [26] pointed out that the response of the pulmonary artery to increased blood flow decreased and showed a reduction of caliber extensibility of the vessel wall by denervation. On the other hand, Veith[10] reported that anastomotic stenosis of the pulmonary artery is the main cause of hypertension of the pulmonary artery. However Fujimura[27] pointed out that pulmonary hypertension was evidenced even by exclusion of anastomotic stenosis.

In this study, it is confirmed that pulmonary hypertension in a donor lung eliminates with time and return to the normal on day 14. It is suggested of vasospasm by Tsuji[20] or edematous change of endothelial cells and basement membran by Shirakusa[23], reflecting denervation or ischemic changes in a donor lung.

Hemodynamic changes in the pressure of the pulmonary artery and increased PVR recovered to 6-7 weeks as reported by Fujimura[20] and to 6-8 weeks as cited by Wagner[29]. It is clarified that regeneration of interrupted nerve fiber is seen in 32 months as the mass of nerve fibers across the bronchial anastomosis line but there is no recovering of Hering-Breuer reflex response by Portin[30], on the other hand, it is reported by Fujimura[31] that there is no sign of nerve regneration with elapsing 6 years of time.

In this study, it is accepted that changes of a donor lung in hemodynamics are influential on denervativn, ischemia, reperfusion response, lymph congestion by interruption of lymphatic channels, lung edema in early stage.

Chest x-ray film is of great benefit to evaluate aeration of a donor lung. Stiegel[17] in dicated a most valuable finding of infiltrative shadow and air-bronchogram to know the function of transplanted lungs, which was appearing on day 1 to 3 and disappearing on day 7 to 21. Kawahara[12] also reported a valid sign of diffuse haziness on chest x-ray film.

In this study, the finding of chest x-ray film coincided with gas exchange and hemodynamics functions of a donor lung.

Storaged donor lung at 4℃ for 6 hours showed the histologic finding of interstitial edema which was appearing the 3rd day after transplantation. It is considered that these changes in acute phase is based on interstitial derangement of extracellular fluid rather than alveolar edema, Veith[32] indicated that a limitation of storage at room temperature is a 4 hour. duration.

In this study, it is certified that cooling at 4 ℃ makes it possiible to elongate the safty storage time to 6 hours.

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