Acta Medica Okayama

Volume 47, *Issue* 5 1993 *Article* 7

OCTOBER 1993

Evaluation of the viability of the canine cadaver lung for transplantation.

Koichi Kayano* Hiroshi Date† Koji Uno‡

Nobuyoshi Shimizu** Shigeru Teramoto††

*Okayama University,

†Okayama University,

‡Okayama Univerisity,

**Okayama University,

††Okayama University,

Evaluation of the viability of the canine cadaver lung for transplantation.*

Koichi Kayano, Hiroshi Date, Koji Uno, Nobuyoshi Shimizu, and Shigeru Teramoto

Abstract

We evaluated the viability of the cadaver lung and the effect of lung inflation with 100% oxygen using a canine allotransplantation model. Donor animals were killed by potassium chloride (KCl) injection and were kept at room temperature until lung extraction. The animals were divided into the following 3 groups: group 1 (n = 6) in which the donor lungs were retrieved 2h after sacrifice, group 2 (n = 6) in which the donor lungs were retrieved 3h after sacrifice, and group 3 (n = 6) in which the donor lungs were retrieved 3h after sacrifice as in group 2 except that they were kept inflated for 3h with 100% oxygen using a double lumen endotracheal tube. Heparin was not given and lungs were not flushed with preservation solution. After left lung transplantation, the transplanted lung function including gas exchange and pulmonary hemodynamics was assessed for 6h by ligating the right pulmonary artery of the recipient animals. All 6 animals in groups 1 and 3 survived for 6 h with excellent lung function. Only 2 of 6 animals in group 2 survived for 6h with poor lung function. These results led us to conclude the following: a) the cadaver lung kept at room temperature for 2h might be available for lung transplantation, and b) when the cadaver lung is inflated with 100% oxygen, the length of safe ischemic time could be prolonged up to 3h.

KEYWORDS: cadaver lung, single lung transplantation, ?lung inflation

---

*PMID: 8273456 [PubMed - indexed for MEDLINE]

Acta Med Okayama 47 (5) 329-337 (1993)

Evaluation of the Viability of the Canine Cadaver Lung for Transplantation

Koichi Kayano*, Hiroshi Date, Koji Uno, Nobuyoshi Shimizu and Shigeru Teramoto

Second Department of Surgery, Okayama University Medical School, Okayama 700, Japan

We evaluated the viability of the cadaver lung and the effect of lung inflation with 100% oxygen using a canine allotransplantation model. Donor animals were killed by potassium chloride (KCl) injection and were kept at room temperature until lung extraction. The animals were divided into the following 3 groups: group 1 (n = 6) in which the donor lungs were retrieved 2h after sacrifice, group 2 (n = 6) in which the donor lungs were retrieved 3h after sacrifice, and group 3 (n = 6) in which the donor lungs were retrieved 3h after sacrifice as in group 2 except that they were kept inflated for 3h with 100% oxygen using a double lumen endotracheal tube. Heparin was not given and lungs were not flushed with preservation solution. After left lung transplantation, the transplanted lung function including gas exchange and pulmonary hemodynamics was assessed for 6h by ligating the right pulmonary artery of the recipient animals. All 6 animals in groups 1 and 3 survived for 6h with excellent lung function. Only 2 of 6 animals in group 2 survived for 6h with poor lung function. These results led us to conclude the following: a) the cadaver lung kept at room temperature for 2h might be available for lung transplantation, and b) when the cadaver lung is inflated with 100% oxygen, the length of safe ischemic time could be prolonged up to 3h.

Key words: **cadaver lung, single lung transplantation, lung inflation**

In the United States and Europe, clinical lung transplantation has been widely performed for several years with excellent outcomes (1). However, the scarcity of appropriate pulmonary donors remains a serious problem. Legal restrictions and medical logistics make it difficult to perform lung transplantation from a brain dead donor in Japan at this time. Therefore, if a cadaver lung could be made available for lung transplantation, it would increase the pulmonary donor pool and would overcome the delays posed by the legal issue of brain death. The tolerance of the lung against warm ischemia has been studied by a number of investigators (2-4), mostly using an autotransplantation model of living animals. They reported the length of safe warm ischemic time ranged from 30 min to 4 h. The tolerance to warm ischemia differs among organs. All organs except the lung depend on blood circulation for cellular respiration. Because the lung structure is so unique that its cellular respiration can occur directly across a gas interface, it is the only organ which can maintain its aerobic metabolism without blood circulation by using the oxygen in the alveoli (5), and therefore might be stronger than other organs against warm ischemia.

In this study, we evaluated the viability of the cadaver lung and the effect of lung inflation with 100% oxygen using a canine left lung allotransplantation model.

Materials and Methods

Eighteen pairs of mongrel dogs (weighing 8.0 to 12.0 kg) were used for the left lung allotransplantation. Donor dogs were premedicated with intramuscular injection of ketamine (8 mg/kg) and atropine sulfate (0.05 mg/kg), and anesthetized with intravenous thiopental sodium (20 mg/kg). The animals were intubated and mechanically ventilated with room air. Tidal volume was set at

* To whom correspondence should be addressed.

20 ml/kg, and respiratory rate 15 breaths/min. To measure the lung temperature of the donor, a temperature probe was placed in the middle lobe of the right lung through a mini-thoracotomy. After closure of the right chest, the donors were sacrificed by an intravenous injection of KCl 10 ml without heparinization. They were replaced in a supine position with all limbs tied to an animal board and were kept at room temperature for 2 or 3 h, during which time the lung temperature was measured every 10 min. Then, a double lung block was extracted from the donor through a median sternotomy while leaving the trachea clamped, and cooled in saline ice. The left lung was trimmed from the double lung block for subsequent transplantation.

The donor animals were arbitrarily assigned to one of the following 3 groups. In group 1 ($n = 6$), the donor lungs were retrieved 2 h after sacrifice, and in group 2 ($n = 6$), they were retrieved 3 h after sacrifice, none were inflated. In group 3 ($n = 6$), the donor lungs were retrieved 3 h after death as in group 2 except that they were kept inflated (PEEP = 15 cm H_2O) with continuous humidified 100 % oxygen flow using a double lumen endotracheal tube. At the time of donor lung extraction, the lungs appeared dark and deflated in groups 1 and 2, whereas the lungs in group 3 looked pink and well inflated (Fig. 1). In all groups, fresh thrombus was always detected in the left artium and in the pulmonary artery and it was removed before transplantation.

The recipient animals were sedated in the same manner as described for the donors. Anesthesia was maintained with a 50:50 mixture of nitrous oxide/oxygen and 0.5 % to 1.0 % halothene. A Swan-Ganz catheter was positioned in the main pulmonary artery through the external jugular vein or the right femoral vein to measure pulmonary arterial pressure (PAP), central venuos pressure (CVP), and cardiac output (CO). A percutaneous femoral arterial monitoring line was inserted to measure aortic pressure (AoP) and blood gas analysis. Then, a thoracotomy was performed in the left fifth intercostal space followed by pneumonectomy of the left side. The right pulmonary artery was encircled with a silk string for the measurement of left lung function after transplantation.

The left lung transplantation was performed following the method of previously described technique (6), with anastomoses first of left atrium, then the pulmonary artery, and finally the bronchus. During implantation, the donor lung was wrapped in cold gauze. During the bronchial anastomosis, the endotracheal tube was advanced into the right main bronchus and then returned to its mid-tracheal position after completion of the anastomosis. Just before completion of the suture of the pulmonary artery, the left atrial clamp was opened and the pulmonary artery was flushed

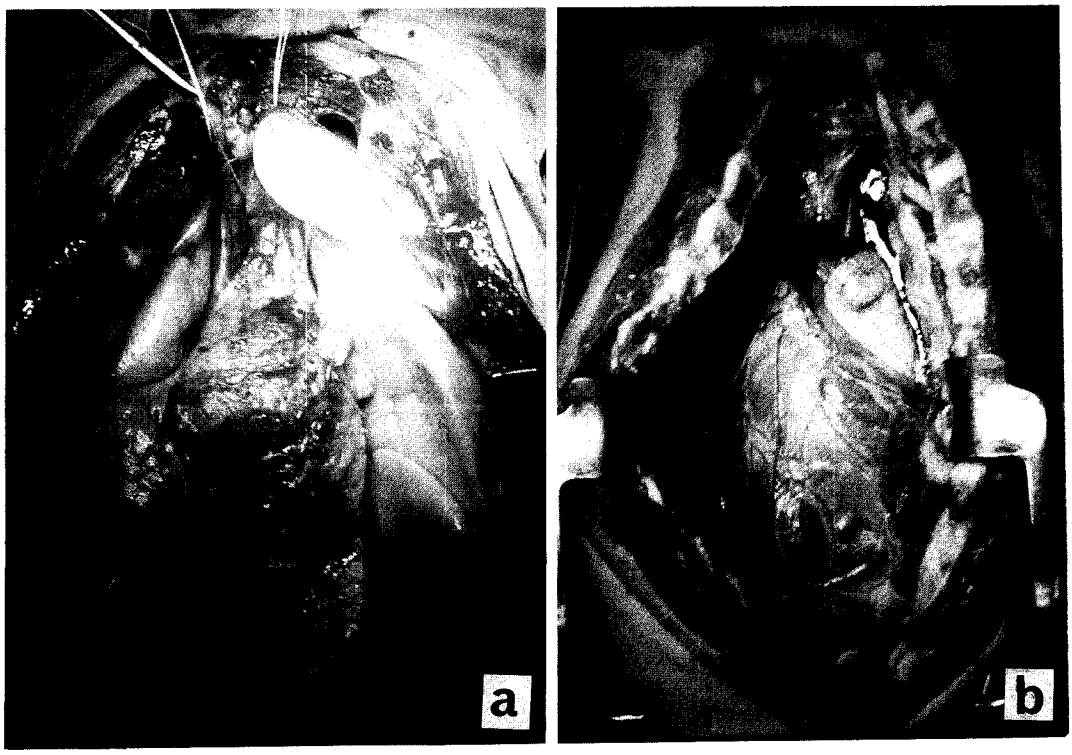

Fig. 1 Donor lung appearance at the time of the extraction. **a**: These lungs are inflated with oxygen and look pink. **b**: These lungs are deflated and appear dark.

to remove any air.

After transplantation, both lungs were ventilated with a tidal volume of 20 ml/kg, a positive endo-expiratory pressure of 5 cm H_2O, at a respiratory rate of 15 breaths/min and an inspired oxygen fraction of 1.0. Systemic, pulmonary and central venous pressure (AoP, PAP, CVP) were continuously recorded. Cardiac output (CO) was determined in triplicate by the thermodilution method. Arterial blood gases were measured periodically. After the baseline measurement (BL), the right pulmonary artery was ligated so that all pulmonary flow was diverted to the transplanted left lung alone while both lungs were ventilated. The recipients depended on only the transplanted lung for blood gas exchange. The animals were observed for 6 h or until death, during which time the left lung function was repeatedly measured at specific intervals (5, 10, 30 min, 1, 2, 3, 4, 5, 6 h after the ligation of the right pulmonary artery). The survivors were killed at 6 h.

If metabolic acidosis occurred, sodium bicarbonate was infused intravenously to maintain the base excess between 0 and 5 mEq/l. If respiratory acidosis occurred, the respiratory rate of the ventilator was increased to 20 breaths/min. However, the respirator rate was decreased to at least 15 breaths/min before assessment. The transplanted lungs of all recipients were retrieved at the time of death or at the completion of the 6 h assesment. Specimens of the left middle lobe were fixed by inflation with and immersion in formalin, embedded in paraffin, and stained with hematoxylin and eosin for subsequent histological examination. Specimens of the left upper and lower lobes were used to measure the wet/dry ratio which was determined by the weight difference between specimens before and after being dried for about 3 weeks in an oven kept at 70–90 °C.

Statistical analysis was performed using analysis of variance (ANOVA). Results are presented as mean ± standard deviation. Probability values less than 0.05 were considered significant.

Results

Harvesting time, treatment time and operating time were similar among the 3 groups (Table 1). Harvesting time was defined as the time needed to extract the donor lung. The treatment time was defined as the time needed to trim the left lung from the double lung block in cold saline. Operating time was defined as the time needed to implant the left lung. Transplantation procedures usually required 1–1.5 h. Warm ischemic time (WIT) was defined as the time from death until the beginning of the lung extraction. Total ischemic time (TIT) was defined as the time from death until blood flow was restored to the transplanted lung.

Lung temperature. Changes in the donor lung temperature after sacrifice are shown in Fig. 2. The mean room temperature for group 1 was 23.1 ± 1.4 °C, 23.9 ± 1.3 °C for group 2, and 23.4 ± 0.9 °C for group 3, and did not differ significantly among the 3 groups. Although the lung temperature fell in all groups, it was significantly lower in group 3 than in groups 1 and 2 ($p < 0.05$). The final temperature at the beginning of the donor lung extraction were 34.2 ± 0.9 °C in group 1, 32.4 ± 1.6 °C in group 2, 28.9 ± 1.1 °C in group 3, which were still much higher than the room temperature. The difference between groups 2 and 3 was only about 3 °C.

Survival. Survival rate for the 6 h assessment

Table 1 Time schedule from the donor sacrifice until completion of the transplantation procedure

Required time (min)	Group 1 (n = 6)	Group 2 (n = 6)	Group 3 (n = 6)
Warm ischemic time	123.8 ± 3.6	181.1 ± 2.6	182.6 ± 3.4
Harvesting time	8.7 ± 5.5	8.6 ± 5.4	10.0 ± 1.9
Treatment time	13.0 ± 7.2	9.3 ± 4.4	9.0 ± 4.0
Operating time	70.2 ± 11.4	62.3 ± 6.5	60.2 ± 2.7
Total ischemic time	212.3 ± 8.2	261.5 ± 6.2	264.6 ± 7.4

Results are expressed as the mean ± SD in each group.
Donor (dog) lungs were retrieved 2 h (Group 1) and 3 h (Group 2) after sacrifice without inflated. The lungs were kept inflated with 100 % oxygen for 3 h after sacrifice and were retrieved (Group 3).

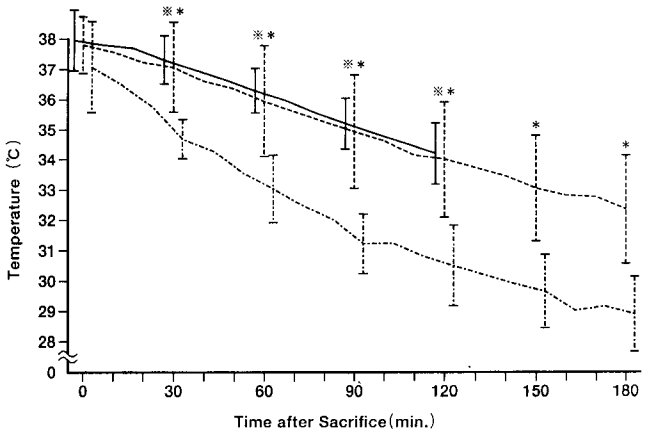

Fig. 2 Changes in the lung temperature during the warm ischemic time measured by the temperature probe in the right middle lobe of the donor lung. Lung temperature in group 3 is always lower than in other groups. Three hours after sacrifice, the lung temperature in group 2 is 32.4 ± 1.6 °C and that in gruop 3 is 28.9 ± 1.1 °C. The difference is about 3 °C. Group 1(——), Group 2(·····), Group 3(-·-·-). *$p < 0.05$ (Group 1 *vs* Group 3), *$p < 0.05$ (Group 2 *vs* Group 3).

period is shown in Fig. 3. All recipient animals in groups 1 and 3 survived during the observation period with excellent gas exchange function and hemodynamics. In contrast, only 2 of the 6 recipient animals in group 2 survived with poor lung function. Each of the 4 remaining animals in this group died of lung edema in 9, 16, 235 and 300 min, respectively, after ligation of the right pulmonary artery. The mean survival time in groups 1 and 3 was exactly 360 ± 0 min, but the mean survival time in group 2 was 213 ± 148 min. The mean survival time in group 2 was significantly shorter than in groups 1 and 3 ($p < 0.01$).

Gas exchange and hemodynamics. Changes in arterial oxygen tension (PaO_2) of the survivors before and

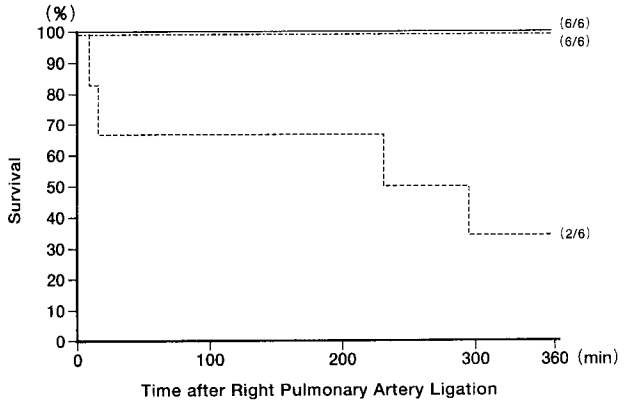

Fig. 3 Survival curves of recipients. Survival rate in group 2 is significantly lower than others. Mean survival time in group 2 is significantly shorter than others. All recipents in groups 1 and 3 survived during the 6 h observation period. Mean survival time; 360 ± 0 min (Group 1) (——); 213 ± 48 min* (Group 2, $*p < 0.01$ Group 2 *vs* Groups 1 and 3) (·····); 360 ± 0 min (Group 3) (-·-·).

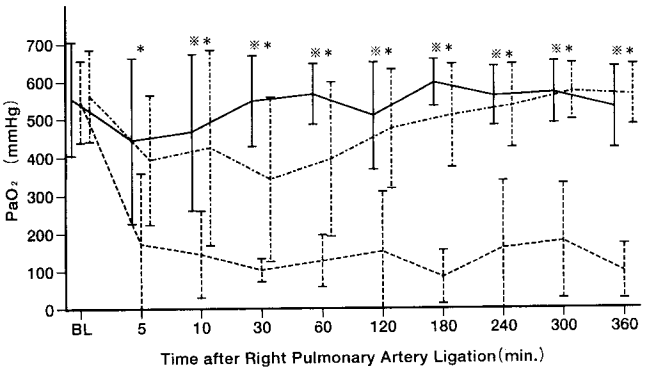

Fig. 4 Postoperative changes in arterial oxygen tension (PaO_2) for recipients of three groups. BL = baseline. The PaO_2 values in groups 1 and 3 are significantly higher than that in group 2 at any time after transplantation. Group 1(——), Group 2(·····), Group 3(-·-·). $*p < 0.05$ (Group 2 *vs* Group 1), $*p < 0.05$ (Group 2 *vs* Group 3).

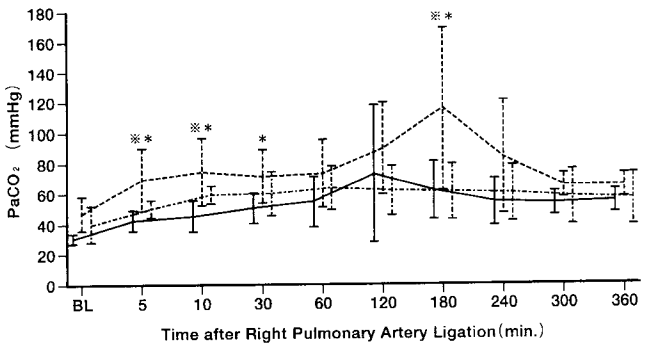

Fig. 5 Postoperative changes in arterial carbon dioxide tention ($PaCO_2$) for recipiests of three groups. The $PaCO_2$ values in group 2 are significantly higher than in groups 1 and 3 for the intial 30 min after right pulmonary artery ligation. And those in group 2 tended to be slightly higher than others at other times. Group 1(——), Group 2(·····), Group 3(-·-·). $*p < 0.05$ (Group 2 *vs* Group 1), $*p < 0.05$ (Group 2 *vs* Group 3).

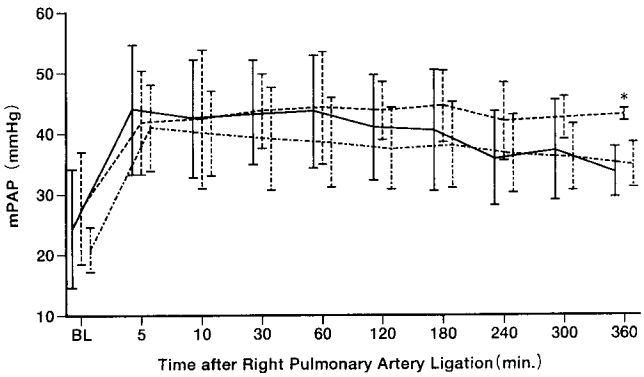

Fig. 6 Postoperative changes in mean pulmonary artery pressure (mPAP) for recipients of three groups. The mean PAP values are not significantly different except the last assessment. That in group 2 was stable, whereas those in groups 1 and 3 gradually decreased. Group 1(——), Group 2(·····), Group 3(-·-·). $*p < 0.05$ (Group 2 *vs* Groups 1 and 3).

after ligation of the right pulmonary artery are shown in Fig. 4. PaO_2 in group 2 dropped dramatically soon after single lung perfusion and was significantly lower than in groups 1 and 3 during the 6 h assessment period. The PaO_2 after 6 h of single lung perfusion was 530.6 ± 108.1 mmHg in group 1, 96.8 ± 73.8 mmHg in group 2, and 564.4 ± 81.2 mmHg in group 3 ($p < 0.05$, group 2 versus groups 1 and 3). The values in groups 1 and 3 were similar to those before ligation of the right pulmonary artery (baseline = BL). A transient drop in PaO_2 during the initial 30 min was observed in group 3, although the drop was not statistically significant. The maximal depression in PaO_2 was apparent by the first 30 min, and PaO_2 had gradually improved and usually reached baseline levels. This phenomenon was probably due to intravascular thrombosis, because heparin was not administered in this study. The PaO_2 values immediately after single lung perfusion correlated well with the survival of the animals. All dogs except the one in which the PaO_2 exceeded 150 mmHg at 30 min after ligation of the right pulmonary artery survived during the 6 h observation period.

Changes in arterial carbon dioxide tension ($PaCO_2$) are shown in Fig. 5. $PaCO_2$ in group 2 increased significantly by ligation of the right pulmonary artery and was significantly higher than in groups 1 and 3 after 5, 10, 30 and 180 min, of single lung perfusion.

Changes in mean pulmonary arterial pressure (mPAP) are shown in Fig. 6. The mean PAP increased about 1.7 times by ligation of right pulmonary artery in all 3 groups. It was stable in group 2 during the observation period, while it was decreased gradually without reaching the baseline in groups 1 and 3. The mPAP after the 6 h single lung perfusion was 33.8 ± 4.1 mmHg in group 1, 43.0 ± 1.0 mmHg in group 2, and 34.8 ± 3.7 mmHg in group 3 ($p < 0.05$, group 2 versus groups 1 and 3).

CO was stable in all 3 groups and did not differ significantly among them (Fig. 7).

Wet and dry ratio. The wet/dry ratios of the transplanted lung after 6 h of single lung perfusion or at death were 5.59 ± 0.86 for group 1, 8.79 ± 1.78 for group 2, and 5.42 ± 0.62 for group 3. The wet/dry ratio

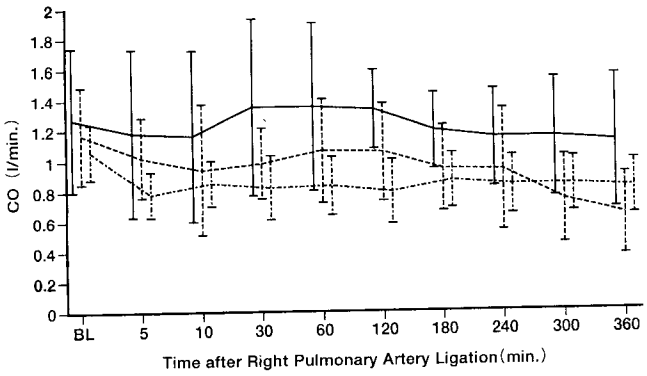

Fig. 7 Postoperative changes in cardiac output for recipients. There was no significant difference among 3 groups. Group 1(——), Group 2(·····), Group 3(-·-·).

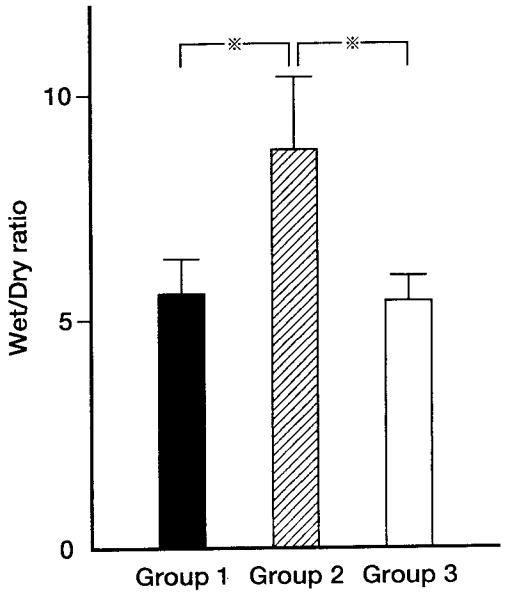

Fig. 8 The wet/dry ratio of the transplanted lung. The wet/dry ratio in group 2 is clearly significantly bigger than others. $*p < 0.01$.

Table 2 Changes in histological findings in transplanted lung tissues at 6 h or death after transplantation

Histological findings	Group 1 (n = 6)	Group 2 (n = 6)	Group 3 (n = 6)
Congestion	N.C.	+++	N.C.
Alveolar edema	N.C.	+++	+
Perivascular edema	++	++	++
Abrasion of bronchial mucosa	N.C.	+	N.C.
Alveolar emphysema	+	N.C.	++

No change (N.C.), mild (+), moderate (++), and severe (+++) degeneration compared with normal tissues. Groups are the same as those listed in Table 1.

in group 2 was significantly higher than in the other two groups ($p < 0.01$, Fig. 8).

Histology. Microscopic examination of the lung in group 2 carried out at 6h after transplantation and at death, showed a typical picture of congestion and extensive pulmonary parenchymal edema as well as thrombus formation and perivascular hemorrhage (Fig. 9 a, b). The proteinaceous exudate was extensive and diffuse in some cases, with complete obliteration of the alveolar spaces and loss of the alveolar architecture (Fig. 9c). Abrasion of bronchial mucosa and subpleural edema (Fig. 9d) were present in group 2. In contrast, these changes

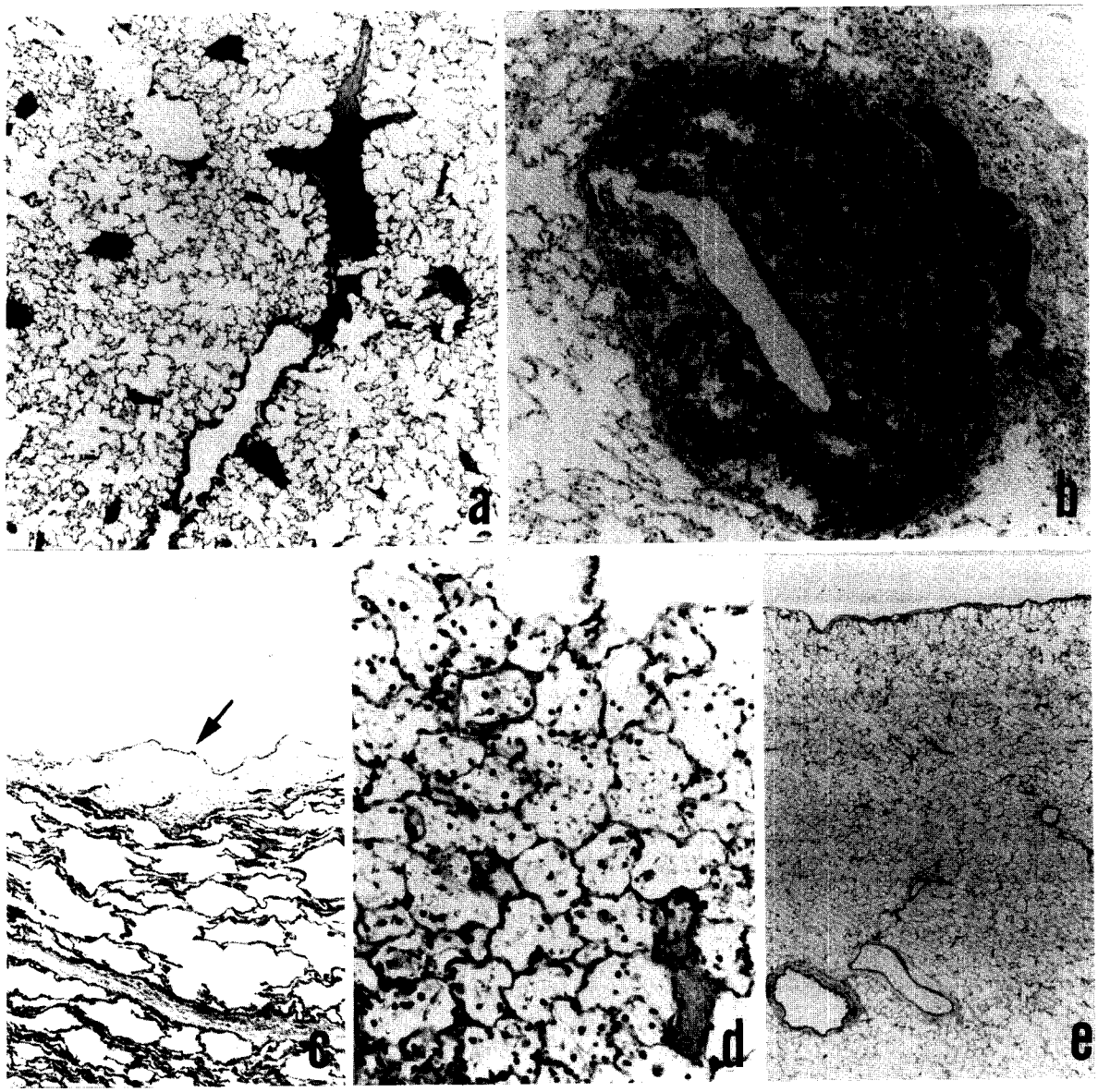

Fig. 9 Histological examination of the transplanted lung, excised at the time of death or at 6h following the occlusion of the right pulmonary artery. **a**: Typical congestion and thrombus formations exist in group 2. **b**: Severe perivascular hemorrhage exists in group 2. **c**: Severe proteinaceous exudate exists in pulmonary alveolar spaces. **d**: Subpleural space is filled exudate. That is called subpleural edema. **a**)~**d**) photoes belong to group 2. **e**: Fewer areas of congestion are found than in group 1. This belongs to group 3.

were not as marked in group 1 or 3. A typical picture of minimal congestion was shown in a few areas (Fig. 9e). The histological findings are summarized in Table 2.

Discussion

Lung transplantation has been widely accepted as an effective therapy for various end-stage lung diseases. However, the scarcity of satisfactory pulmonary donors is an increasingly serious problem. One of the strategies to increase the size of the pulmonary donor pool is the use of cadaver lungs for transplantation. Harvesting lungs from cadavers after cessation of blood circulation would also overcome the difficulties related to the issue of brain death in Japan. Cadaver lung transplantation is based on the notion that lung tissue can maintain its cellular respiration by using the oxygen in the alveoli even after cessation of circulation, and pulmonary cellular elements may remain viable for a certain period after cardiac arrest.

A number of investigators have conducted examinations on the lung's tolerance of warm ischmia. In 1953, Blades *et al.* (2) reported that temporary occlusion of the left pulmonary vessels and bronchial arteries for varying periods of time up to 6h produced astonishingly little gross or microscopic change in pulmonary tissue. Their studies suggested that 30min appeared to be the upper limit of any appreciable survival of lung function in a dog. Arnar *et al.* (7) subjected baboons to lung reimplantation with periods of ischemia extending up to 4h in 1967. Unfortunately, these reports did not evaluate the function of the lung exposed to warm ischemia because the contralateral native lung was left in place. Homatas *et al.* (8), working with excised lungs, showed that the lungs which were artificially ventilated in the cadaver for up to 6h subsequently provide adequate gas exchange. They used heparin and flushing in their experiments. In 1971, Joseph and Morton (9) demonstrated that immediate and total respiratory function could be obtained in baboons after 4h of normothermic ischemia with the lung inflated, following the autotransplantation of the left lung and immediate contralateral pulmonary artery ligation. Using a canine left lung autotransplantation model, Yamazaki *et al.* (10) clearly demonstrated that the maximum length of tolerable WIT of the deflated canine lung was considered to be 120min by ligating the right pulmonary artery. These previous studies have suggested that the lung can remain viable for a certain period at warm temperature after cessation of circulation.

A study on cadaver lung transplantation was first reported by Egan *et al.* (11) in 1991. In their study, donor dogs were killed and the subsequent lung harvest was delayed for 1, 2, or 4h. Pulmonary retrieval was then performed after flushing the lungs with modified Euro-Collins solution, and the lungs were stored for 4h before left lung allotransplantation. They reported that all recipient animals of 1h cadaver lungs survived the 8h observation period with excellent hemodynamics and gas exchange after occlusion of the pulmonary artery and bronchus to the native lung. Another excellent investigative series on cadaver lung transplantation were published by Ichinose *et al.* (12, 13) in 1992. They reported that the lung of donors with non-beating dog hearts could tolerate up to 3h of WIT for transplantation without flushing, and that it could be transplanted after a 2h period of warm ischemia and 24h of preservation with Ep4 solution following intravenous administration of methylpredonisolone and heparin. Although their study provided us with much useful information, they did not assess the lung function immediately after transplantation, which we believe to be essential for evaluating the viability of the cadaver lung. Yamazaki *et al.* (10) also reported that the survival of the animals following right pulmonary artery ligation was closely associated with the PaO_2 values immediately after the operation, but was unrelated to the changes in pulmonary arterial pressure.

The present study was undertaken to answer the following questions: a) How long is a safe warm ischemic period for cadaver lung transplantation without any treatment to the donor? b) Is it possible to prolong this safe WIT by inflating the lung with 100% oxygen?

Based on the results from groups 1 and 2, the length of safe WIT appears to be around 2h when no treatment is given to the donor. Because extraction and implantation take approximately 1.5h, the length of safe TIT is around 3.5h. Ischemia that is extended beyond the length of tolerance produces irreversible damage to the pulmonary parenchyma, resulting in greater capillary permiability. All animals in group 1 survived during the 6h observation period with excellent lung function, but 4 of the 6 animals in group 2 died of edema of the lung. Since we ligated the right pulmonary artery to divert all pulmonary blood flow through the transplanted lung alone while both lungs were ventilated, the conditions of assessment of the viability of the cadaver lung were more than simply physiological. The respiratory function of the recipient in our experiment

deteriorated when the vital capacity of the transplanted lung was decreased gradually due to edema after reperfusion. The increase in $PaCO_2$ values observed in both groups 1 and 2 after ligation of the right pulmonary artery reflected preferential ventilation to the more compliant native lung, which acted like dead space. This phenomenon was not observed in Egan *et al.* report because the right main bronchus was also occluded (11). Therefore, it was possible to evaluate the compliance of the transplanted lung by measuring the $PaCO_2$ in our model. Significantly, the higher $PaCO_2$ in group 2 indicated a lower compliance of the lung in group 2 than in group 1. PaO_2 which we believe is the most reliable indicator for evaluating lung function remained over 450 mmHg throughout the observation period despite some increases in $PaCO_2$ in group 1. This excellent result in group 1 was also confirmed histologically.

It is evident that inflation of the cadaver lung with 100 % oxygen prolongs the length of safe WIT. The lung function in group 3 was much better than in group 2, and was comparable to that in group 1. This may be due to the physical stretching of the alveoli, providing ischemic lung tissue with more oxygen, lowering lung temperature by increasing the contact surface of the lung tissue with the air. In 1971, Veith *et al.* (3) reported that an inflated lung functioned better than a deflated one in a canine model. Weder *et al.* (5) found that preservation with 100 % oxygen inflation appeared superior to inflation with room air and much better than with 100 % nitrogen inflation in a paracorporeal circulation rabbit model. Data *et al.* (14) clearly demonstrated that lung cells were able to maintain aerobic metabolism utilizing the oxygen in the alveoli during preservation, and that the maintenance of aerobic metabolism may be essential to maintain the optimum viability of preserved lung tissue. Lungs in group 2 looked dark and almost completely deflated at the time of excision, indicating a state of anaerobic metabolism. In contrast, lungs in group 3 looked pink and well inflated, indicating a state of aerobic metabolism.

Lung temperature was lowered significantly by inflating the lung with oxygen. However, the difference between groups 2 and 3 after a 3 h period of warm ischemia was only about three degrees and the temperature was still close to 30 °C in group 3. Therefore, it was likely that the effect of oxygen inflation was not due to lower lung temperature. In fact, in our extra experiment, even when the lung was inflated through the trachea with cool air (1 °C), the lung temperature was almost similar to room temperature. Whether cooling the cadaver lung by ventilation with cold air or lowering the cadaver temperature itself would have a protective effect is an interesting question that should be investigated in future studies.

Our results regarding the wet/dry ratio were significantly higher in group 2 than in groups 1 and 3. The wet/dry ratio corresponded well to both the respiratory function and histology. The wet/dry ratio generally represents the severity of lung edema caused by the increase of capillary permeability after a certain ischemic period.

Inflating the cadaver lung with 100 % oxygen is a simple process requiring intubation with a double lumen endotracheal tube and continuously supplying oxygen. This method could be easily performed during the time needed to obtain permission for the donation from the family and during transportation. Most of the cadaver lungs expected to become available for lung transplantation would be obtained from individuals killed in accidents or who die suddenly outside of a hospital. It would be difficult to add any pretreatment to the donor in such circumstances. For this reason, heparin was not administered to the canine donor before sacrifice in our study. A transient drop in PaO_2 during the initial 30 min observed in group 3 may be due to microcoagulation in the pulmonary capillaries. As Egan *et al.* reported, pulmonary flushing with optimal preservation solution at the time of harvest may flush out the microcoagulation and improve lung function after transplantation (11). The length of safe WIT of the cadaver lung in our study was approximately 2 h when deflated, and about 3 h when inflated with 100 % oxygen, which may not be long enough to apply this method to a clinical situation. Nevertheless, the possibility of cadaver lung transplantation demonstrated in this study is most encouraging.

In conclusion, the cadaver lung kept at room temperature for 2 h may be available for lung transplantation, and the length of safe WIT may be prolonged up to 3 h if the cadaver lung is inflated with 100 % oxygen.

Acknowledgments. We gratefully acknowledge the expert technical assistance of Mr. T. Kawakami.

References

1. Cooper JD, Pearson FG, Patterson GA, Todd TRJ, Ginsberg RJ, Goldberg M and Demajo WAP: Technique of successful lung transplantation in human. J Thorac Cardiovasc Surg (1987) **93**, 173-181.

2. Blades B, Pierpont HC, Samadi A and Hill RP: The effect of experimental lung ischemia on pulmonary function: A preliminary report. Surg Form (1953) **4**, 255–260.
3. Veith FJ, Sinha SBP, Graves JS, Boley SJ and Dougherty JC: Ischemic tolerance of the lung: The effect of ventilation and inflation. J Thorac Cardiovasc Surg (1971) **61**, 804–810.
4. Stevens GH, Rangel DM, Yakeishi Y, Sanchez MM and Fonkalsrud EW: The relationship of ventilation to preservation of the ischemic canine lung graft. Curr Top Surg Res (1969) **1**, 51–66.
5. Weder W, Harper B, Shimokawa S, Miyoshi S, Date H, Schreinemarkers H, Egan T and Cooper JD: Influence of intraalveolar oxygen concentration on lung preservation in a rabbit model. J Thorac Cardiovasc Surg (1991) **101**, 1037–1043.
6. Keshavjee SH, Yamasaki F, Cardoso PF, McRitchie DI, Patterson GA and Cooper JD: A method for safe twelve-hour pulmonary preservation. J Thorac Cardiovasc Surg (1989) **98**, 529–534.
7. Arnar O, Anderson RC, Hitchcock CR and Haglin JJ: Reimplantation of the baboon lung after extended ischemia. Transplantation (1967) **5**, 929–935.
8. Homatas J, Bryant L and Eiseman B: Time limits of cadaver lung viability. J Thorac Cardiovasc Surg (1968) **56**, 132–140.
9. Joseph WL and Morton DL: Influence of ischemia and hypothermia on the ability of the transplanted primate lung to provide immediate and total respiratory support. J Thorac Cardiovasc Surg (1971) **62**, 752–761.
10. Yamazaki F, Wada H, Aoki M, Inui K and Hitomi S: An evaluation of the tolerance of the autotransplanted canine lung against warm ischemia. Jpn J Surg (1989) **19**, 326–333.
11. Egan TM, Lambert CJ, Reddick R, Ulicny KS, Keagy BA and Wilcox BR: A strategy to increase the donor pool: Use of cadaver lungs for transplantation. Ann Thorac Surg (1991) **52**, 1113–1121.
12. Ichinose T, Handa M, Matsumura Y, Sasaki H, Okada Y and Fujimura S: Hypothermic preservation of the transplanted lung from non-heart beating donors in dogs. Jpn J Transplant (1992) **27**, 300–308.
13. Ichinose T, Handa M, Matsumura Y, Sasaki H, Okada Y and Fujimura S: Transplantation of the lung from non-heat beating donors in dogs. Jpn J Transplant (1992) **27**, 209–315.
14. Date H, Matsumura A, Manchester JK, Cooper JM, Lowry OH and Cooper JD: Changes in alveolar oxygen and carbon dioxide concentration and oxygen consumption during lung preservation. J Thorac Cardiovasc Surg (1993) **105**, 492–501.

Received March 29, 1993; accepted May 28, 1993.