

Efficacy of Modified University of Wisconsin Solution for 24-Hour Preserved Canine Lung

Nobufumi SASAKI

The First Department of Surgery, Nagasaki University School of Medicine, Nagasaki, Japan

A 24-hours cold preserved lung using a low potassium UW solution (4 mEq/L or 30 mEq/L) was experimentally allotransplanted on dogs and subsequently the grafts function was carefully evaluated. Twenty-three adult mongrel dogs underwent thoracotomy by median sternotomy and pulmonary function was evaluated after the right bronchus and the right pulmonary artery were clamped. And then the both lungs and heart were flushed through the pulmonary artery with 50 ml/kg of modified UW solution at a pressure of 10-14 mmHg; Group 1 (n=7), grafted lungs were flushed and preserved with original UW solution ($[K^+]=120$ mEq/L); Group 2 (n=10), a donor lungs were flushed and preserved with modified UW solution ($[K^+]=30$ mEq/L); Group 3 (n=6), the lungs were preserved with extracellular type UW solution ($[K^+]=120$ mEq/L) after flushing. The left lung was allografted after 24-hour cold preservation. During storage, the lung was inflated. Graft function was evaluated one hour after reperfusion and prior to sacrifice. The dogs were sacrificed between 4 days and 4 weeks after transplantation. Mean cold ischemia and warm ischemia times were 24.2 ± 0.4 hours and 71.5 ± 14.2 min, respectively. Flushing time was longer in Group 1 (287.3 ± 107.0 sec) than in any other group (160.0 ± 107.0 sec in Group 2, 163.2 ± 58.3 sec in Group 3), but there was no significant difference among the groups. Two of the 7 dogs in Group 1, 2 of the 10 dogs in Group 2 and 4 of the 6 dogs in Group 3 did not survive more than 3 days. The Pa O₂, lung water content, and dynamic compliance showed no significant difference among the groups. The static compliance at one hour after reperfusion was 15.43 ± 2.88 ml/cmH₂O in Group 1, 19.46 ± 3.12 ml/cmH₂O in Group 2 and 17.21 ± 3.12 ml/cmH₂O in Group 3. The Cst at one hour after reperfusion was higher in Group 2 than in Group 1 ($P < 0.05$). The PVR increased to 2339.9 ± 623.3 dyne · sec · cm⁻⁵ in Group 1, 1365.3 ± 482.3 dyne · sec · cm⁻⁵ in Group 2 and 2051.1 ± 278.2 dyne · sec · cm⁻⁵ in Group 3. The PVR was lower in Group 2 than in Group 1 ($P < 0.05$) at one hour after reperfusion. In conclusion, the modified UW solution containing the potassium concentration of 30 mEq/L is suitable to the original UW solution ($[K^+]=120$ mEq/L) or extracellular type UW solution ($[K^+]=4$ mEq/L) for the 24-hour cold preservation of canine lung allografts.

INTRODUCTION

The first lung transplantation was performed in 1963. Since immunosuppressive therapy was developed, lung

transplantation has become confirmed as a therapy for patient suffering from the end of lung disease. However, lung transplantation has many restricting factors, the suitable storage of donor lung was one of them. The donor lung storage was limited to four to six hours by means of immerse cooling¹⁾ and the exploitation and development of the more beneficial methods for long-term storage have been required.

The University of Wisconsin (UW) solution was one of the most useful preservation solution for organ transplantation. Experimentally, the mean preservation time of the liver²⁾, the pancreas³⁾, and the kidney⁴⁾ has been extended to 48 hours and/or 72 hours with UW solution respectively. Previously, we reported that beneficial preservation of canine lung for 24 hours was achieved with UW solution⁵⁾⁶⁾ and availability of low potassium UW solution containing potassium of 30 mEq/L has been elucidated for 24 hours cold preservation by using canine isolated lung reperfusion model⁷⁾. In this study, allotransplantation of a 24-hour cold preserved lung by using low potassium UW solution was experimentally performed and graft function was prudently evaluated.

MATERIALS AND METHODS

(1) Study groups

Twenty-three pair adult mongrel dogs weighting 7-13 kg were included in this study. The dogs were supplied by Laboratory Animal Center for Biochemical Research of Nagasaki University School of Medicine. All animals received human care in compliance with the "Guide for the Care and Use of Laboratory Animals of Nagasaki University".

The dogs were classified into three groups: Group 1 (n=7), the grafted lungs were flushed and preserved with original UW solution ($[K^+]=120$ mEq/L); Group 2 (n=10), the grafted lungs were flushed and preserved with modified UW solution ($[K^+]=30$ mEq/L); Group 3 (n=6), the grafted lungs were in the same maneuver with extracellular type UW solution ($[K^+]=4$ mEq/L). The

Table 1. Composition of Preservation Solution

	UW [K+] = 120 mEq/L	UW [K+] = 30 mEq/L	UW [K+] = 4 mEq/L
K lactobionate	100 mM	-	-
Na lactobionate	-	100 mM	100 mM
KH ₂ PO ₄	25 mM	25 mM	4 mM
NaH ₂ PO ₄ · 2H ₂ O	-	-	21 mM
MgSO ₄ · 7H ₂ O	5 mM	5 mM	5 mM
Raffinose	30 mM	30 mM	30 mM
Glutathione	3 mM	3 mM	3 mM
Adenisine	5 mM	5 mM	5 mM
Allopurinol	1 mM	1 mM	1 mM
Penicillin G	200,000 U/L	200,000 U/L	200,000 U/L
Insulin	100 U/L	100 U/L	100 U/L
Hydroxyethyl starch	50g/L	50g/L	50g/L
Na ⁺	30±2 mEq/L	130±7 mEq/L	143±4 mEq/L
K ⁺	121±3 mEq/L	29±1 mEq/L	4±0.4 mEq/L
Osmotic pressure	320±9 mOsm/L	342±11 mOsm/L	339±14 mOsm/L
pH (room temp.)	7.40	7.40	7.40

components of preservation solution are tabulated in Table 1.

(2) Anesthesia

All animals were anesthetized with intravenous administration of pentobarbital of 25 mg/kg (Nenbutal injection (R)) and intubated. The dogs were ventilated at a fixed FIO₂ of 1.0, tidal volume of 35 ml/kg and respiratory rate of 14 breath/min using Harvard Ventilator. A 5 Fr thermodilution catheter (TD catheter, TERUMO) was introduced from the jugular vein to main pulmonary artery (PA), and another 5 Fr thermodilution catheter (Nihon Kodon Co.) for measurement of lung water content was placed to the abdominal aorta through the femoral artery.

(3) Unilateral pulmonary artery occlusion test (UPAO test)

The pulmonary function was estimated after occlusion of right PA and right main bronchus by clamps because of direct evaluation for grafts. Animals were measured blood gas analysis, PA pressure, left atrial (LA) pressure, peak airway pressure, end-inspiratory pressure, extravascular lung water content and cardiac output (CO), and calculated dynamic lung compliance (C_{dy}), static lung compliance (C_{st}) and pulmonary vascular resistance (PVR). The pressure was measured by using polygraph RMP 6004S (Nihon Kodon Co.), the CO was calculated by the thermodilution meter MTC-6100 (Nihon Kodon Co.) and extravascular lung water content (ELWC) was calculated by the lung water computer (Nihon Kodon Co.).

(4) Donors procedure

Donor dogs were anesthetized as described before. Animals had thoracotomy by median sternotomy and both

side PA and the right main bronchus were isolated. After the tidal volume was changed from 35 ml/kg to 25 ml/kg, the right PA and right bronchus were clamped, UPAO test was performed as described above.

After declamping, the tidal volume was changed to 35 ml/kg and sling loop was passed around the main PA. Then heparin (500 U/kg) and Prostaglandin E₁ (100 μg/body) were administered through the right ventricle to the main PA. Ten minutes later, the superior and the inferior venacavae and both the subclavian arteries were ligated. A 24 Fr catheter was introduced to the main PA and the sling loop was ligated and both lungs were flushed through the main PA with 50 ml/kg of the 4-8°C UW Solution of each a concentration of potassium at a pressure of 10-14 mmHg. The left atrium was opened to permit drainage of the perfused solution. During flushing, the lungs were ventilated. The heart and the lungs were excised en block, the tracheal tube was inserted into the trachea and then lungs were inflated at fixed FIO₂ of 1.0 and clumped. Then those were put in a sterile vinyl bag filled with the same cold storage solution and stored at 4-8°C for 24 hours in a refrigerator.

(5) Recipients procedure

Twenty-four hours later, recipient dogs were anesthetized as described before and intubated. The submucosal blood flow of the carina and left second carina were measured by laser doppler flow meter Model ALF2100 (Advance Co.) under the right lateral position, then left thoracotomy was performed. The pericardium at the pulmonary hilum was incised, the left PA, the left pulmonary vein (PV) and the left bronchus were divided distal to the hilum for left pneumonectomy. The right PA and the right bronchus were isolated for UPAO test.

Then the preserved heart and the lungs were taken out from refrigerator, the left lung was trimmed for

transplantation, the left PA was divided long and the left bronchus was separated as keeping 2 rings, and the left atrium was trimmed to form the atrial cuff. In a recipient dog, the left PA, the left atrium, and the left bronchus were clamped and left pneumonectomy was performed. The atrial cuff was sutured with 5-0 Prolene (Ethicon Inc.) in a fashion of horizontal everting mattress suture. The PA was sutured with 6-0 Prolene using a over and over continuous running suture technique. The bronchus was sutured with 4-0 Prolene in the same manner.

After all anastomosis, the clamps were released and reperfusion was started. Sixty minutes later, UPAO test was performed. Then the specimen of the left lower lobe were obtained for histological examination. After hemostasis was insured, a 20 Fr thoracic drainage tube was placed for evacuation and the thorax was closed. Then bronchial submucosal blood flow was measured and the L/C ratio (left second carinal submucosal blood flow/carinal submucosal blood flow) was calculated.

(6) Post-operative care

The thoracic drainage tube was removed after air leakage subsided, and all animals were extubated after awaking from the anesthesia. Prophylactic antibiotics, 1 g of cefems, was administered subcutaneously and immunosuppressant, 15 mg/kg of Cyclosporine, was administered intramuscularly every day from the day of surgery until sacrificed.

The dogs were sacrificed between 4 days and 4 weeks after transplantation. Before sacrifice, the measurement of submucosal blood flow, UPAO test and histological examination were performed.

(7) Statistical analysis

All values are given as mean \pm standard deviation. Statistical evaluation was made using the non-parametric multiple comparison test (DUNNET) among the groups. A P value less than 0.05 was considered statistically significant.

RESULTS

(1) Preservation time

Mean cold ischemic time and warm ischemic time were 24.2 ± 0.4 hours and 71.5 ± 14.2 min, respectively. Flushing time were longer in Group 1 (287.3 ± 107.0 sec) than in other groups (160.0 ± 67.5 sec in Group 2, 163.2 ± 58.3 sec in Group 3). There were not significant differences in each groups (Table 2).

(2) Survival rate

Two of the 7 dogs in Group 1, two of the 10 dogs in Group 2 and four of the 6 dogs in Group 3 didn't survive more than 3 days. Two dogs in Group 2 died of rejection and mediastinitis on postoperative day 26 and 19 respectively. Six dogs in Group 2 were sacrificed 7-14 POD. One dog in Group 3 failed to tolerate a UPAO test because of severe lung edema, and a UPAO test was achieved in only one dog in Group 3 at sacrifice (Table 3).

Table 3. Survival Time

Group 1	2d, 2d, 5d*, 7d*, 7d*, 7d*, 7d*,
Group 2	2d, 2d, 7d*, 7d*, 7d*, 9d*, 14d*, 14d*, 19d, 26d,
Group 3	0d, 1d, 2d, 2d, 7d, 7d*,

* Sacrificed and UPAO test could be performed.

(3) Pulmonary function

There was not statistically significant difference in PaO₂ among groups before storage (390.3 ± 105.9 mmHg in Group 1, 360.3 ± 115.1 mmHg in Group 2, 417.6 ± 187.9 mmHg). PaO₂ at one hour after reperfusion was 241.1 ± 124.1 mmHg in Group 1, 213.8 ± 152.2 mmHg in Group 2 and 252.6 ± 170.9 mmHg in Group 3. PaO₂ was decreased after reperfusion, but not significant. There was no significant difference among groups. On 7POD, PaO₂ was 259.7 ± 188.2 mmHg in Group 1, 230.7 ± 156.1 mmHg in Group 2 and 342.7 mmHg in Group 3, significant difference was not appreciated (Fig.1). There was no significant difference in PaCO₂ among groups and there was no time-course change in PaCO₂ during the experiment.

PAP was ranged from 12.0 to 26.8 mmHg prior to storage, there was no significant difference among groups. After reperfusion, PAP was increased gradually. But there

Table 2. Flushing Time, Cold Ischemic Time and Warm Ischemic Time

	Group 1 [K ⁺]=120 mEq/L	Group 2 [K ⁺]=30 mEq/L	Group 3 [K ⁺]=4 mEq/L
Flushing Time	287.3 ± 107.0 sec	160.0 ± 67.5 sec	163.2 ± 58.3 sec
Cold Ischemic Time	23.9 ± 0.4 hr	24.2 ± 0.3 hr	24.3 ± 0.4 hr
Warm Ischemic Time	76.4 ± 9.2 min	66.5 ± 17.0 min	73.7 ± 10.3 min

was no statistical difference between each groups and before and after reperfusion (Fig.2). In each group, there was no significant difference in the LAP before storage, at one hour after reperfusion, and at sacrifice.

ELWC before storage was 4.77 ± 2.33 ml/kg in Group 1, 4.08 ± 1.04 ml/kg in Group 2 and 3.27 ± 1.68 ml/kg in Group 3, respectively. At one hour after reperfusion, ELWC was 10.06 ± 1.85 ml/kg, 10.33 ± 6.13 ml/kg and 10.55 ± 2.85 ml/kg, respectively. On 7POD, ELWC was 8.83 ± 4.41 ml/kg in Group 1, 6.98 ± 0.45 ml/kg in Group 2 and 4.78 ml/kg in Group 3, respectively. There was no significant difference of ELWC among groups (Fig.3).

Before storage, Cdy was 15.33 ± 3.45 ml/H₂O in Group 1, 16.16 ± 4.42 ml/H₂O in Group 2, 15.89 ± 2.85 ml/H₂O in Group 3. After reperfusion, Cdy was decreased to 11.56 ± 1.08 ml/H₂O, 12.09 ± 2.99 ml/H₂O, 12.31 ± 2.36 ml/H₂O, respectively. At 7POD, Cdy was 8.05 ± 3.24 ml/H₂O in Group 1, 7.35 ± 1.78 ml/H₂O in Group 2, Cdy was decreased as time course. There was no significant difference of Cdy among the groups. There was no significant difference of Cst before storage; 19.53 ± 2.34 ml/H₂O in Group 1, 21.87 ± 4.54 ml/H₂O in Group 2 and 21.63 ± 2.98 ml/H₂O in Group 3. At one hour after reperfusion, Cst was 15.43 ± 2.88 ml/

H₂O, 19.46 ± 3.12 ml/H₂O and 17.21 ± 3.12 ml/H₂O respectively. Cst in Group 2 was significant higher than that in Group 1 ($P < 0.05$). On 7POD, Cst was 12.73 ± 3.09 ml/H₂O, 23.25 ± 5.76 ml/H₂O and 18.61 ml/H₂O respectively. There was no statistical significance in each group (Fig.4).

Before storage, there was no significant difference in PVR among groups; 1519.9 ± 446.2 dyne \cdot sec \cdot cm⁻⁵, 1120.6 ± 226.6 dyne \cdot sec \cdot cm⁻⁵, 1479.3 ± 700.1 dyne \cdot sec \cdot cm⁻⁵, respectively. After reperfusion, PVR was increased to 2339.9 ± 623.3 dyne \cdot sec \cdot cm⁻⁵, 1365.3 ± 482.2 dyne \cdot sec \cdot cm⁻⁵ and 2051.1 ± 278.2 dyne \cdot sec \cdot cm⁻⁵, respectively. PVR in Group 2 was significantly lower than that in Group 1 ($P < 0.05$). On 7POD, PVR was 2440.5 ± 867.4 dyne \cdot sec \cdot cm⁻⁵ in Group 1, 2366.5 ± 720.7 dyne \cdot sec \cdot cm⁻⁵ in Group 2 and 2698.3 dyne \cdot sec \cdot cm⁻⁵ in Group 3, there was no significant difference among groups (Fig.5).

L/C ratio before storage was 0.929 ± 0.139 in Group 1, 1.061 ± 0.104 in Group 2 and 0.921 ± 0.046 in Group 3, After reperfusion, L/C ratio was decreased to 0.451 ± 0.069 , 0.537 ± 0.103 and 0.416 ± 0.0613 respectively. At sacrifice, L/C ratio was 0.536 ± 0.085 in Group 1, 0.576 ± 0.218 in Group 2

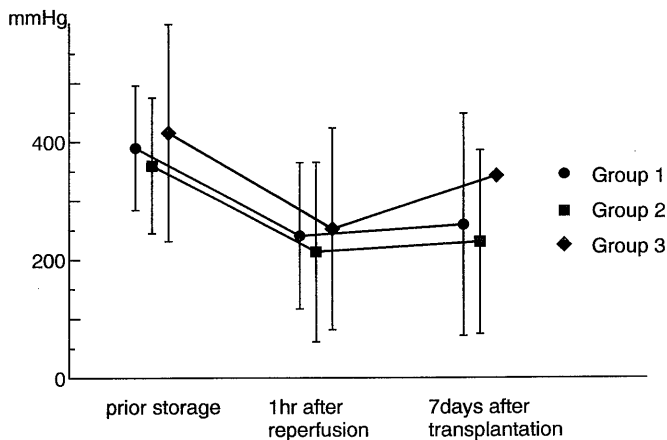


Fig. 1. Arterial Oxygen Pressure

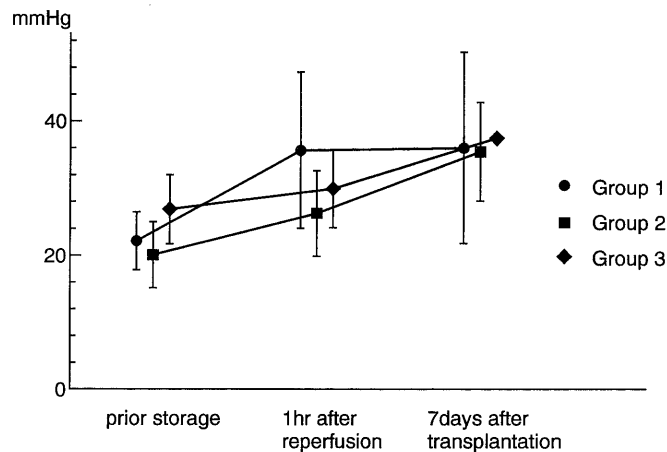


Fig. 2. Pulmonary Artery Pressure

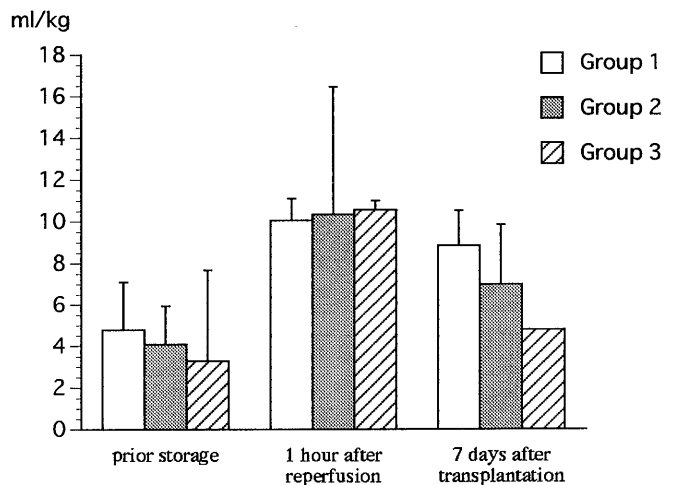
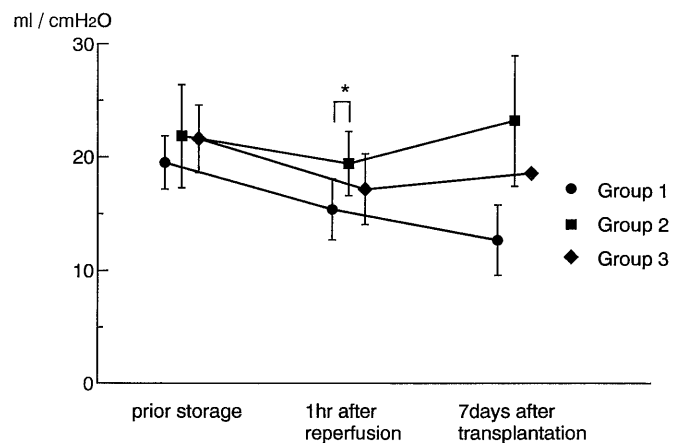


Fig. 3. Extravascular Lung Water Content



* Group 1 vs Group 2 ; $P < 0.05$

Fig. 4. Static Compliance

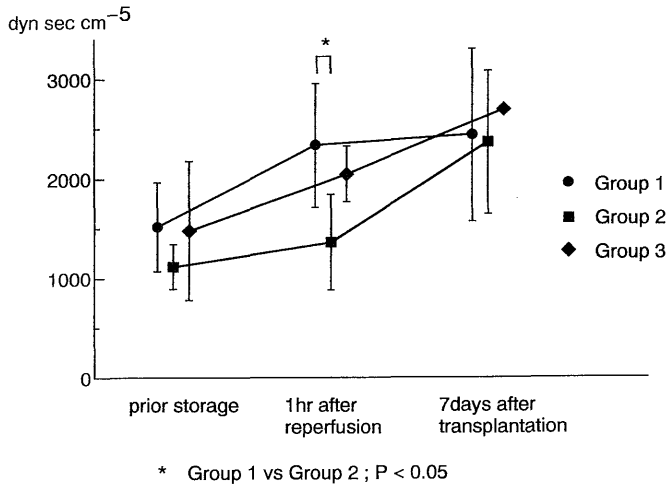


Fig. 5. Pulmonary Vascular Resistance

and 0.437 in Group 3. There was no significant difference in L/C ratio among the groups.

Histologically grafted lungs in Group 1 and 2 revealed mild perivascular edema at 1 hour after reperfusion. Interstitial edema was slightly stronger in Group 3 than in the other groups. Alveolar architecture showed almost normal appearance (Fig.6). The lungs in the dogs that died within 3 days after transplantation showed severe alveolar and perivascular edema and marked vascular congestion.

The lungs at sacrifices showed a varying variety of the degree of alveolar edema and congestion. The lung in one dog in Group 1 that was sacrificed on 7POD showed Grade

I rejection and the lung in the dog in Group 2 died on 26 POD showed Grade II rejection. No evidence of rejection was revealed in the lungs of the other dogs.

DISCUSSION

Development of preservation solution is very important for prolongation of preservation time for organ transplantation. Collins reported that intracellular type solution with high potassium and low sodium prevented cell swelling and potassium ion leakage from preserved cell⁸⁾. Belzer analyzed the necessitating condition of successful cooling storage that 1) hypothermic-induced cell swelling during storage should be inhibited at the minimum, 2) intracellular acidosis should be avoided, 3) the expansion of the interstitial space should be prevented at an initial stage of the storage, 4) injury from oxygen free radical should be minimized, 5) preservation solution should be containing substrates for regenerating high-energy phosphate compounds⁹⁾. On the basis of background for above consideration, UW solution was developed in 1986. Clinical introduction of UW solution for liver, pancreas, and kidney transplantation extended the time limits of successful preservation¹⁰⁾. For lung transplantation UW solution obtained successful preservation¹¹⁾¹²⁾¹³⁾.

But high-potassium concentration are known to cause intense pulmonary vasospasm¹⁴⁾. This constriction seemed to be caused by an influx of calcium through a high

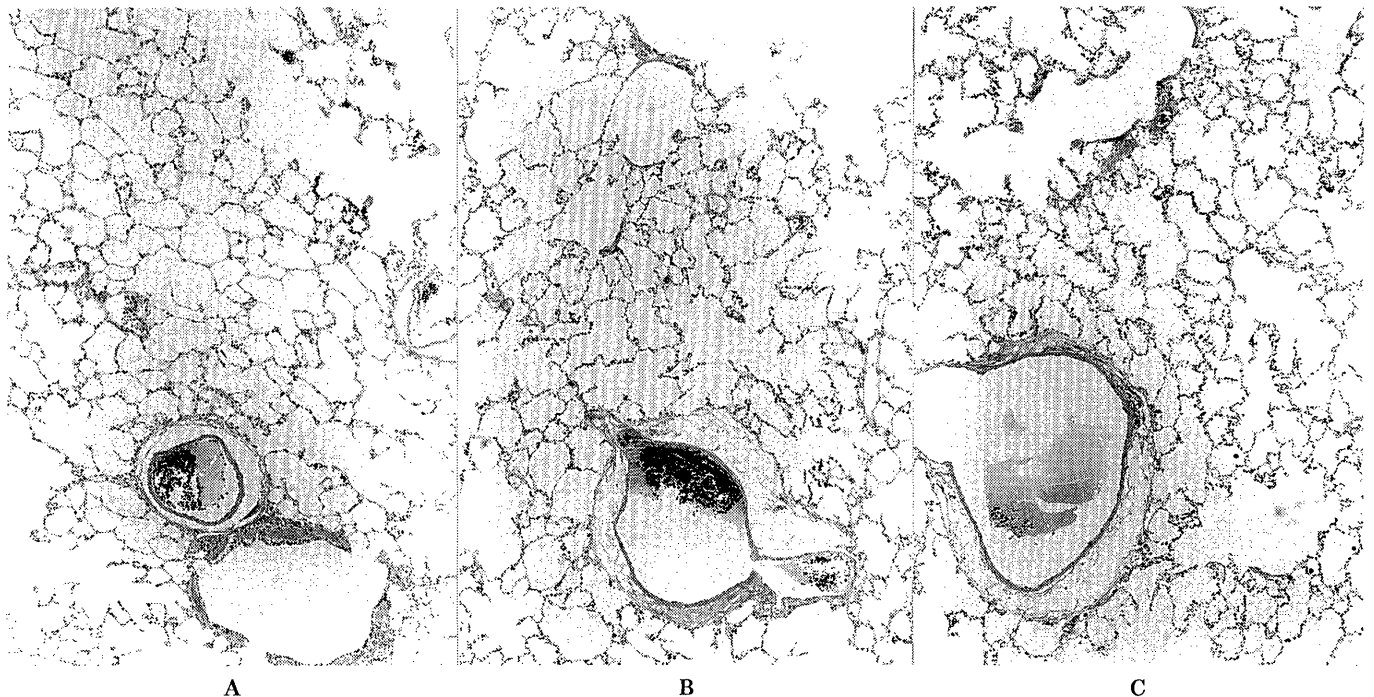


Fig. 6. The photographs of lung in Group 1 (A), in Group 2 (B) and in Group 3 (C) at 1 hour after reperfusion (H-E stain, $\times 20$). Group 1 and Group 2 revealed mild perivascular edema ut alveolar architecture showed almost normal. In Group 3 interstitial edema was slightly stronger than other groups.

potassium-induced depolarizing cell membrane which activated the slow calcium channel¹⁵⁾. There is a belief that flush solution of high potassium concentration caused vasoconstriction and produced uneven distribution of the graft¹⁶⁾. And we used the Prostaglandin E₁ (PG E₁) as vasodilator before harvesting. The use of PG E₁ serves as uniform flush out of graft, and also application of 100 μ g / body of PG E₁ is not small dose for canine when compared with 500 μ g of PG E₁ for human lung transplantation. Vasoconstriction due to 120 mEq/L potassium concentration may exceed the effect of PGE₁.

The PVR values were kept lower in the lungs preserved with modified UW solution ($[K^+]=30$ mEq/L) rather than those with original UW solution ($[K^+]=120$ mEq/L) at one hour after reperfusion ($P<0.05$). Oka and colleagues reported that the mean PAP was significantly higher in the lungs preserved with high potassium UW solution than those with low potassium UW solution ($[K^+]=9$ mEq/L) in isolated rabbit lung reperfusion model despite administration of PG E₁ prior to harvest¹⁷⁾. High potassium concentration crystalloid cardioplegic solutions ($[K^+]=40$ mEq/L) caused vascular damage possibly involving the endothelium or its function compared with low potassium concentration cardioplegic solution ($[K^+]=25$ mEq/L)¹⁸⁾. A high concentration of potassium ion in a preservation solution caused damage to the endothelium in canine liver, kidney and pancreas transplant model¹⁹⁾. In this study, modified UW solution ($[K^+]=30$ mEq/L) was effective in maintaining lower PVR at an early phase after transplantation.

Cst in the lungs preserved with modified UW solution ($[K^+]=30$ mEq/L) was significantly higher than original UW solution at one hour after reperfusion ($P<0.05$). It may be related to production of surfactant. Hachida and colleagues reported that glucose-insulin-potassium solution ($[K^+]=40$ mEq/L) had minimized toxic effect on isolated alveolar type II cells compared with Collins solution and Collins-Sacks solution ($[K^+]=115$ mEq/L)²⁰⁾. This finding may be caused by that alveolar type II cell is maintained in suitable condition and ability of surfactant production is maintained.

Fujimura and colleagues reported that extracellular type solution was superior preservation to intracellular type solution for 24-hour canine lung preservation²¹⁾. Yamasaki and colleagues described that extracellular type solution was superior to Euro-Collins solution ($[K^+]=115$ mEq/L) for rabbit lung preservation²²⁾. Miyoshi and colleagues showed that lung preservation using low potassium UW solution ($[K^+]=4$ mEq/L) was superior to that using high potassium UW solution in absence of vasodilator²³⁾. Experimentally, the efficacy of low potassium UW solution for renal, hepatic, pancreas and cardiac preservation has been demonstrated¹⁹⁾²⁴⁾. In this study, canine lungs preserved with extracellular type UW solution ($[K^+]=4$ mEq/L) maintained lung function at one hour after

reperfusion as well as the lungs preserved with modified UW solution ($[K^+]=30$ mEq/L), but only one dog had tolerated the UPAO test on 7 days after transplantation. Previous study demonstrated that the wet/dry ratio in reperfused lung preserved by extracellular type UW solution was significantly larger than that in lungs preserved by the modified UW solution in isolated canine lung reperfusion model⁷⁾. A graft preserved with modified UW solution is a key of the success of lung transplantation.

In conclusion, the modified UW solution, 30 mEq/L potassium concentration, is superior to intracellular type UW solution ($[K^+]=120$ mEq/L) or extracellular type UW solution ($[K^+]=4$ mEq/L) for maintaining function of a 24-hour preserved canine lung after reperfusion.

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