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Heart and lung preservation using a new solution; UCLA Formula

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Abstract. Heart and lung preservation is a significant barrier in clinical heart and lung transplantation. In a previous study, we have shown that UCLA Formula, modified from cardioplegic solution, has a favorable effect on lung preservation. In this study, we evaluated the effect of the simultaneous flushing method using UCLA Formula alone on both heart and lung preservation. We conducted six experiments using 18 mongrel dogs, weighing 20–28 kg. In the donor animals, the heart and lungs were each flushed with 500 ml of cold UCLA Formula, using two catheters, one inserted into the ascending aorta and the other into the main pulmonary artery. After the heart and lung block was trimmed, orthotopic cardiac transplantation and single left lung transplantation were independently performed on different recipients following preservation for 4.3 h in the case of the heart and 7.5 h in the case of the lung. Thus, the function of the preserved organs was independently assessed using cardiac output and left ventricular end-diastolic pressure (LVEDP) with constant central venous pressure (CVP) in heart transplantation, and arterial gas analysis and the relationship between inspiratory pressure and expiratory tidal volume in lung transplantation. These measurements were performed before harvesting and 1 h and 4 h after transplantation. After heart transplantation cardiac output showed no significant deterioration. No significant differences in gas analysis and the pressure-volume curve were seen after lung transplantation. In conclusion, the simultaneous flushing method using the UCLA Formula may offer reliable preservation for both heart and lung in preparation for transplantation.

Key words: Heart transplant – Lung transplant – Organ preservation

The greatest single problem facing combined heart and lung transplantation is the shortage of suitable donor organs. In particular, the difficulty of prolonged preservation of the heart and lung is a major barrier for distant donor procurement [1, 2]. Our previous studies have shown that a new solution, UCLA Formula, is effective in prolonging lung preservation up to 12 h [3, 4]. Furthermore, since this solution was originally modified from a cardioplegic solution, it is possible to preserve both the heart and lung by perfusion with the same solution. In this study, we assessed the efficacy of UCLA Formula in prolonging the ischemic time in both heart and lung preservation.

Materials and methods

Eighteen mongrel dogs, weighing from 20–28 kg, were used in this study. Heart and lung grafts were obtained from six dogs. To assess the organ viability following preservation, orthotopic heart transplantation was performed in six dogs and single lung transplantation was performed in the remaining six dogs. The animals were assigned randomly to each experiment.

The donor animals were anesthetized by intravenous administration of sodium pentobarbital, 30 mg/kg. After endotracheal intubation and ventilatory support, a median sternotomy was performed. The heart and both lungs were freed of mediastinal attachments and the animal was given heparin (3 mg/kg). Two catheters were placed into the ascending aorta from the right common carotid artery and the main pulmonary artery. These catheters were connected to bottles containing UCLA Formula. After inflow occlusion was produced and the respirator discontinued, the aorta and trachea were clamped. The heart was perfused with 500 ml of cold UCLA Formula (4 °C) at a pressure of 100 mm Hg, and both lungs were perfused with 500 ml of cold UCLA Formula (4 °C) at 50 cm of H_2O pressure (Fig. 1). A small incision was made in the inferior vena cava and the left atrium to drain the perfused solution. Topical cooling was also applied with ice slush inserted into the chest cavity.

After 5–10 min of perfusion, the carotid arteries were divided and an incision was made in the aortic arch. The incision was carefully extended to the posterior mediastinum and the heart and lung block was excised at both venae cavae, the ascending aorta, and the trachea just above the carina. Subsequently, the heart and lung block was immersed in cold saline (4 °C) and stored in the refrigerator at 4 °C after being double wrapped in a sterile plastic bag. After 4 h of preservation, the heart and lung block was taken out and trimmed for orthotopic heart transplantation. The remaining lungs were fur-

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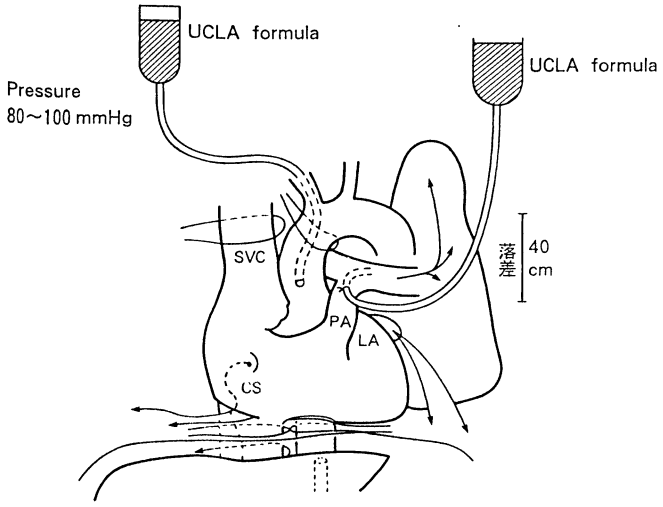


Fig. 1. Experimental model

ther preserved at 4 °C in the refrigerator. Orthotopic heart transplantation was performed in six dogs in the usual manner after the 4 h of preservation. During the surgical procedure, the donor heart was continuously perfused with approximately 200 ml of cold UCLA Formula (4 °C) at 50 cm H_2O pressure.

Single left lung transplantation was performed in six dogs, using the remaining preserved left lung as a donor graft. The surgical technique has been described previously [3]. Throughout the surgical procedure, the lung was wrapped in a cold towel and slowly perfused with approximately 100 ml of UCLA Formula to maintain it at a low temperature and to avoid mechanical damage to the graft. Mean ischemic time was 4.3 h in the heart and 7.6 h in the lung.

Measurements. The viablity of the preserved heart was evaluated by measuring cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP) with a constant central venous pressure (CVP). The pretransplant values were obtained immediately after the median sternotomy was performed on the donor animal. Hemodynamic data including blood pressure, cardiac output, LVEDP, and CVP were measured with the catheter directly introduced into the ascending aorta and left ventricle. A 7F Swan-Ganz catheter was inserted into the main pulmonary artery to measure the cardiac output by the thermo-dilution method and to monitor pulmonary artery pressure. These measurements were performed while the CVP was adjusted to 7 cm H_2O by the use of transfusion and diuretics. Arterial blood gases including pH, oxygen tension (PO_2) and carbon dioxide tension (PCO_2) were examined periodically throughout and after the transplantation.

To assess the preserved left lung viability after the transplantation, blood gas analysis, including PO_2 and PCO_2, and the pulmonary pressure-volume curve with a contra-lateral occlusion test were used as indicators. Each animal was placed on a pressure-controlled respirator (Mark 7, Bird Products, Palm Springs, Calif.) with an inspiratory oxygen fraction (FiO_2) of 0.5. The inspiratory pressure was adjusted to 7, 10, 15, and 20 cm H_2O and the expiratory tidal volume was simultaneously recorded while the right pulmonary artery and bronchus were tightly clamped with a non-clashing vascular calmp. Throughout the operation, approximately 1000 ml of lactated Ringer's solution were infused.

All measurements were repeated at each interval of the preharvesting operation, and at 1 h and 4 h after the transplantation.

Solution. The UCLA Formula used in this study was made in our laboratory prior to each experiment. It contained glucose 50 gm/l regular insulin 80 U/l, NaH_2PO_4 0.6 gm/l, Na_2HPO_4 6.4 gm/l, KCL 1.5 gm/l, Mannitol 2.5 gm/l, autologous serum 30 ml/l, and verapamil 10 mg/l (Table 1). The concentrations of electrolytes in the solution were: Na, 60 mEq/l and K, 30 mEq/l. The pH and osmolarity were 7.4 and 350 mosmol, respectively. The serum used in the solution was derived from blood from the same animal used as a donor.

All results are expressed as mean ± standard deviation of the mean. Paired and unpaired *t*-tests were used to assess statistical significance. Analysis of variance was used to determine the significance of differences between the experimental groups. Differences were considered to be statistically significant at a probability value less than 0.05.

Results

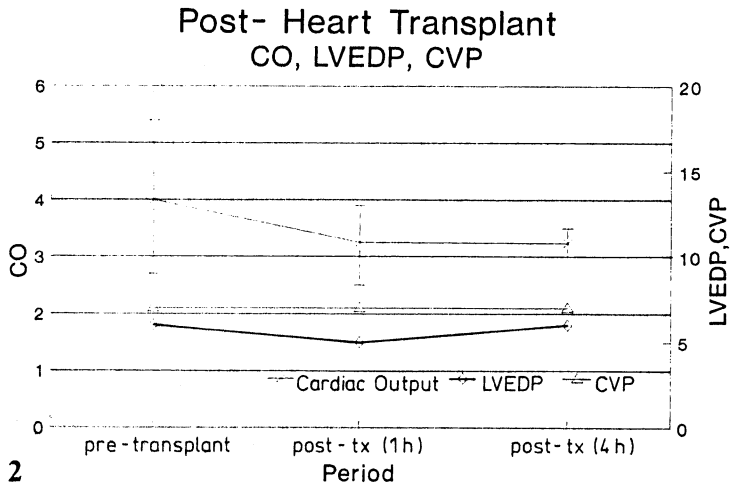
The mean ischemic time was 4.3 ± 0.5 h in the heart and 7.5 ± 0.7 h in the lung. Figure 2 demonstrates the cardiac output, LVEDP and CVP at the pretransplant and postoperative periods. CVP was maintained at 7 cm H_2O during the measurements. Cardiac output was 4.01 ± 1.36 l/min in the pretransplant period, 3.26 ± 0.68 l/min at 1 h, and 3.24 ± 0.26 l/min at 4 h after the heart transplantation these changes were not significant. LVEDP was 7.1 ± 0.8 mm Hg in the pretransplant period, 6.5 ± 0.86 mm Hg at 1 h, and 7.4 ± 1.2 mm Hg at 4 h after the transplantation. These changes were not significant. Thus, there was no significant difference between the pretransplant, and posttransplantation values of cardiac output and LVEDP under constant CVP following 4.3 h of heart preservation in UCLA Formula.

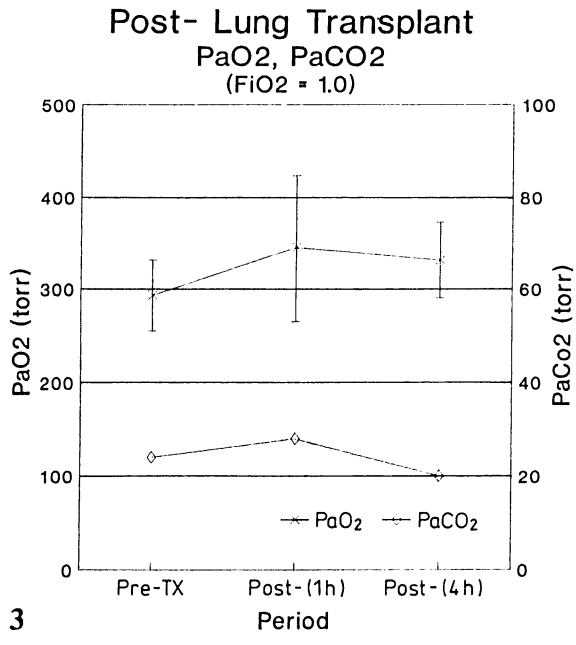
The preserved lung was examined while the left pulmonary artery and bronchus were totally occluded. The PO_2 tension (FiO_2 0.5) was 293.7 ± 38.3 mm Hg in the pretransplant period, 310 ± 62.7 mm Hg at 1 h, and 235.0 ± 87.8 mm Hg at 4 h postoperatively. These changes were not significant (Fig. 3). PCO_2 tension was 24.6 ± 7.2 mm Hg in the pretransplant period, 26.2 ± 9.4 mm Hg at 1 h, and 33.2 ± 9.3 mm Hg at 4 h postoperatively. These changes were not significant. Thus, no significant difference was observed between each period in PO_2 and PCO_2 after lung transplantation following 7.5 h lung preservation in UCLA Formula.

The relationship between inspiratory pressure and expiratory tidal volume was evaluated in each period (Fig. 4). The expiratory tidal volume at a pressure of 20 cm H_2O was 475 ± 55.9 ml in the pretransplant period, 437.0 ± 165.9 ml at 1 h, and 536.7 ± 101.5 ml at 4 h postoperatively; at a pressure of 15 cm H_2O the expiratory tidal volume was 330.0 ± 71.6 ml in the pretransplant period, 352.5 ± 71.6 ml at 1 h, 366.7 ± 54.0 ml at 4 h postopera-

Table 1. Constitution of UCLA Formula

Glucose	(gm/l)	50
Insulin	(U/l)	80.0
Na_2HPO_4	(gm/l)	6.4
NaH_2PO_4	(gm/l)	0.6
KCl	(gm/l)	1.5
Mannitol	(gm/l)	2.5
Verapamil	(mg/l)	10.0
Serum	(ml/l)	30.0
pH		7.4
Na	(mEq/l)	60
K	(mEq/l)	30
Osmolarity	(mosmol)	350





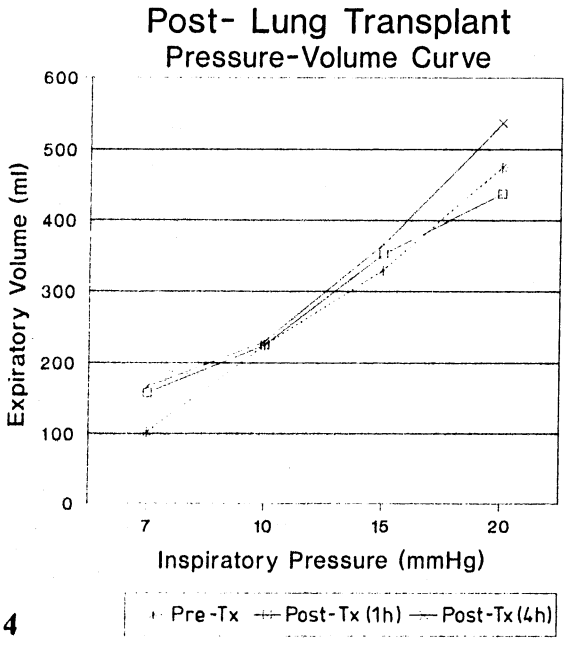


Fig. 2. Assessment of the donor heart preserved with UCLA Formula. Cardiac output and LVEDP were measured with a constant CVP (7 cm H_2O). There was no significant difference between pre- and post-transplantation *(tx)* value (paired and unpaired *t*-test)

Fig. 3. Assessment of the donor lung preservation with UCLA Formula. PO_2, PCO_2 showed no significant deterioration after transplantation *(Tx)* (paired and unpaired *t*-test)

Fig. 4. The relationship between inspiratory pressure and expiratory tidal volume. There was no significant difference between pre- and post-transplantation *(Tx)* values (paired and unpaired *t*-test)

tively; at a pressure of 10 cm H_2O, this was 225 ± 71.2 ml pretransplant, 225.0 ± 94.1 ml at 1 h, and 230.0 ± 46.3 ml at 4 h postoperatively; at a pressure of 7 cm H_2O, this was 102.5 ± 17.8 ml pretransplant, 157.5 ± 99.6 ml at 1 h, and 166.7 ± 51.2 ml at 4 h postoperatively. The tidal volume at each inspiratory pressure was not significantly different among the three groups. Therefore, no significant deterioration was detected in heart and lung following preservation in UCLA Formula.

Discussion

An effective method of organ preservation is crucial for both lung and combined heart-lung transplantation [5–8]. Of the many solutions that have been tested, no solution has been effective in both heart and lung [9]. Up until now, the heart and lung have been independently perfused with different solutions. The lungs could be preserved for 4 h with Euro-Collins' solution, which consists of intra-cellular components. In contrast, approximately 4 h of heart preservation was obtained with various cardioplegic solutions of extra-cellular composition [9]. We can assume that approximately 60 ml of the remaining solution in each lung graft is flushed into the heart after reperfusion, and since extra-cellular solutions contain high amounts of potassium, there may be an unfavorable effect on the donor heart graft. In cases where single lung transplantation and orthotopic transplantation are performed by sharing a heart and lung from the same donor animal, which are preserved using conventional solutions, a similar deteriorating effect may occur in the native heart upon flushing of the remaining solution in the donor lung. As UCLA Formula contains 30 mEq/l of potassium (vs 115 mEq/l in Euro-Collins' solution which is made of intracellular composition) and is beneficial for both heart and lung preservation, the drastic interaction of the different solutions during preservation and the deleterious effect on the heart after the reperfusion might be prevented by using the same extra-cellular solution. Therefore, we

believe that flushing the heart and lungs with the same extracellular solution may be the optimal method for preservation.

The major role of a pulmoplegic solution is to provide prompt hypothermia to the whole lung without toxicity to the various types of specialized cells in the lung tissue. In particular, the effect of solutions on alveolar type II cells are the most critical because these cells play an important role in synthesis, storage, and secretion of the alveolar surfactant [10]. Using the viability of these cells as an indicator, we have investigated the effect of various solutions in vitro [11]. We found that GIK solution, which has been used as a cardioplegic solution, was the most effective solution for the pulmonary alveolar cells. Furthermore, in 1986, we demonstrated the beneficial effect of the Ca channel blocker, verapamil, on lung preservation. In that study, tissue damage caused by ischemia was significantly reduced by adding verapamil [12]. Based upon these experimental experiences, we composed the new solution, UCLA Formula, for lung preservation. Using this solution, 12 h of lung preservation was achieved.

UCLA Formula is based on the GIK (Glucose-Insulin-Potassium) solution, which was originally developed as a cardioplegic solution [13]. The effect of glucose, insulin, and potassium in heart preservation has received much attention over the years. In fact, it has been reported that glucose and insulin enhance the rate of anaerobic glycolysis, reverse ion loss, alter membrane electrophysiologic impairment, decrease plasma free fatty acid concentration, and alter plasma osmolarity. Furthermore, insulin reduces sodium permeability and stimulates active Na ion efflux. Hess and colleagues have suggested that glucose in GIK may also act as a scavenger of oxygen free radicals [14]. Because the energy source of the ischemic lung is exclusively dependent on anaerobic glycolysis, the presence of sufficient glucose in the solution plays an important role in supplying this energy. Because of these beneficial effects, we considered that the GIK solution might be an optimal solution for protecting the ischemic lung from injury. On the basis of these experimental experiences, we used this solution for simultaneous heart and lung preservation in the present study.

To assess the heart and lung function independently following each preservation, we evaluated the heart with orthotopic heart transplantation, and the lung with single lung transplantation using a contra-lateral occlusion test. As a result, the parameters we used in this study showed no significant deterioration in the heart and lung after the preservation. Although we have achieved 12 h of lung preservation using this Formula, the results of the present study suggest that UCLA Formula was effective not only in the lung preservation, but also in heart preservation. In conclusion, the simultaneous flushing method using the UCLA Formula may offer reliable preservation for both heart and lung transplantation. We studied 4 h of heart preservation and 7 h of lung preservation using the UCLA Formula in this study. We will continue to investigate the limitation of preservation time in the heart and lung using UCLA Formula.

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