COMPARISON OF UNIVERSITY OF WISCONSIN, EURO-COLLINS, LOW-POTASSIUM DEXTRAN, AND KREBS-HENSELEIT SOLUTIONS FOR HYPOTHERMIC LUNG PRESERVATION

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Objective: We sought to test the effectiveness of 4 different solutions for hypothermic rat lung preservation.

Methods: One hundred ninety-two rats were used. The rats were divided into 4 groups, and University of Wisconsin, Euro-Collins, low-potassium dextran, or Krebs-Henseleit solution was used in each group. They were further divided into 6 subgroups of 8 rats each. The lungs were preserved at 4°C for 0, 4, 6, 8, 12, or 24 hours, respectively, and lung function was studied by using a living rat perfusion model.

Results: Pulmonary arterial flow decreased in each group after 4 to 6 hours of preservation; the low-potassium dextran group decreased the least and the Krebs-Henseleit group decreased the most. Pulmonary vascular resistance increased in each group after 6 hours of preservation; the Krebs-Henseleit group increased the most. Although airway pressure increased, static lung compliance and gas exchange capacity decreased after 8 hours of preservation; the Krebs-Henseleit group exhibited the worst values. Lung tissue wet/dry weight ratio increased gradually during preservation; the University of Wisconsin group exhibited the least increase. An ultrastructural study indicated the least morphologic changes in the low-potassium dextran group at 24 hours.

Conclusions: At 4°C, all solutions preserved rat lungs for 4 hours with acceptable function. However, 6 hours of preservation resulted in damaged pulmonary function in some lungs, and this damage increased when preservation time was extended. The lungs preserved in low-potassium dextran solution had the best overall function, but the lungs preserved in University of Wisconsin solution had less edema. (*J Thorac Cardiovasc Surg* 2000;119:921-30)

Despite more than 30 years of extensive study, lung preservation time is still very short.¹ The reported effects of currently used solutions for lung preservation vary substantially. This is partly related to the difficulties in lung function tests after preservation. Most experiments only test lung function in a very short time period, such as 10 to 20 minutes.²⁻⁴ Other studies use a

complicated set-up for the tests.⁵⁻⁷ Almost all of these studies investigate lung function after a fixed preservation time. No systematic or ultrastructural studies have been performed in these comparisons. The living rat lung model developed in our laboratory allows an isolated lung to undergo perfusion for 3 to 4 hours. This model has provided a simple and stable set-up for isolated lung function studies. In this study we compared two common intracellular preservation solutions (University of Wisconsin [UW] and Euro-Collins [EC] solutions) with an extracellular preservation solution (low-potassium dextran [LPD] solution) for hypothermic lung preservation. A common extracellular perfusion solution (Krebs-Henseleit [KH] solution) was also used for comparison with the above solutions.

Material and methods

Healthy, adult, Sprague-Dawley rats weighing 250 to 300 g were used for this study. All animals received humane care in compliance with the "Principles of Laboratory Animal Care"

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Fig 1. Living rat perfusion apparatus. The isolated lung is perfused by the blood from the internal jugular vein of the host rat. Blood returned from the isolated lung is collected in the perfusion chamber (C) and reservoir (R) and then returned to the arterial system of the host rat by means of a roller pump. The *open arrow* indicates the direction of flow of nonoxygenated venous blood. The *filled arrows* indicate the direction of flow of oxygenated blood. (From Wu G, Zhang F, Salley RK, Diana JN, Su T-P, Chien S. Delta opioid extends hypothermic preservation time of the lung. *J Thorac Cardiovasc Surg* 1996;111:259-67.)

formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (National Institutes of Health publication No. 86-23, revised 1985).

Solutions used. UW and EC solutions were purchased commercially. LPD and KH solutions were made in our laboratory. The compositions of these solutions are shown in Table I.

Perfusion apparatus. The lung function study was performed as previously described.⁸ Briefly, the isolated lung was suspended in a perfusion chamber. The cap of the perfusion chamber was removable and had a tube for attaching the trachea of the isolated lung. This tube was connected to a rodent respirator (model 683; Harvard Apparatus Co, Inc, S Natick, Mass) for ventilation. On the top of the tube, a Y connector was attached to a Gould pressure transducer (Gould Instrument Systems, Inc, Valley View, Ohio) for measuring respiratory pressure. The cap had another tube connected to the jugular vein of the host rat for perfusion of the pulmonary artery of the isolated lung. A 2-mm flow probe was incorporated into this line and was interfaced with a Transonic T 201 flowmeter (Transonic Systems, Inc, Ithaca, NY) for monitoring the perfusion flow. Venous blood return from the isolated

Table I. Composition of preservation solutions

	UW	EC	LPD	KH
Potassium	125	115	4	5.25
Sodium	30	10	168	150
Calcium	—	—	—	2
Magnesium	5	—	—	1.2
Chloride	—	15	103	131
Phosphate	25	57.5	36.7	1.25
Sulfate	5	—	—	1.2
Glucose	—	196	—	10
Glutathione	3	—	—	—
Dextran 40	—	—	1.25	—
Adenosine	5	—	—	—
Lactobionate	100	—	—	—
Raffinose	30	—	—	—
Allopurinol	1	—	—	—
Dexamethasone	20.3	—	—	—
Hydroxyethyl starch (g/dL)	5	—	—	—
Insulin (U/L)	40	—	—	—
Osmolality (mOsm/L)	320	375	285	312

Concentrations are expressed as millimoles per liter, except where noted.

lung was collected at the bottom of the perfusion chamber and was returned to the left carotid artery of the host rat by using a Minipols roller pump (model 312; Gilson Co, Middleton, Wis). The chamber was heated by a temperature-controlled water bath with a circulating pump maintained at 37°C (Fig 1).

Preparation of the host rat. Anesthesia was induced by means of an intraperitoneal injection of sodium pentobarbital (35-50 mg/kg body weight). The cervical trachea was cannulated. The rats' lungs were ventilated through an endotracheal tube by using a rodent respirator with room air. The tidal volume was 2.5 to 3.5 mL, and the rate was 40 to 50 cycles/min. A 2-mm catheter was inserted into the right jugular vein. Heparin sodium (3 mg/kg) was infused intravenously, and both carotid arteries were cannulated with 0.5-mm catheters. The catheter in the right carotid artery was connected to a Gould pressure transducer for blood pressure monitoring. From the right jugular vein of the host rat, the blood withdrawn by gravity flowed to the perfusion chamber to perfuse the pulmonary artery of the isolated lung. A hydrostatic pressure of 25 mm Hg was maintained by adjusting the height distance between the host rat and the isolated lung. Blood returned from the pulmonary vein of the isolated lung was collected and recirculated, as described earlier. Arterial blood samples were taken from the host rat every 10 minutes for blood gas and electrolyte analysis. The blood return rate, tidal volume, and respiratory rate for the host rat were adjusted to maintain stable arterial blood pressure and arterial blood gas values.

Preparation and preservation of the isolated lung. The lung donor rats were anesthetized by using an intraperitoneal injection of sodium pentobarbital (35-50 mg/kg body weight). The cervical trachea was cannulated, and each animal was ventilated by using a rodent respirator with room air.

A tidal volume of 2.5 to 3.5 mL and a rate of 40 to 50 cycles/min were maintained. An incision was made below the xiphoid process, and the retrosternal space was exposed by means of blunt dissection. Two large straight clamps were attached to the incision to open the chest by means of median sternotomy, avoiding injury to the lungs or great vessels. After intravenous administration of heparin sodium (3 mg/kg), the inferior pulmonary ligaments were carefully divided. The left superior vena cava was then dissected, ligated, and divided. The hilum of the left lung was approached anteriorly, and the vessels and bronchus were separated by using blunt dissection. The left pulmonary artery was dissected, and a suture was placed loosely around it. The main pulmonary artery was then transected through the transverse sinus to allow placement of a cannula in the left pulmonary artery. The loose suture around the left pulmonary artery was tied, and preservation solution was then infused through the cannulated left pulmonary artery. In this study one of the 4 preservation solutions (10-15 mL at 4°C) was flushed through the lung through the pulmonary artery at a gravity gradient of 25 cm H₂O. The left atrium was partially excised for decompression. After being flushed, the lungs were removed and immersed in the preservation solutions before performing function studies. The trachea was clamped at the end of inspiration to maintain inflation (with room air) during the hypothermic storage.

Animal groups studied. One hundred ninety-two rats were used in this study. The animals were randomly divided into 4 main groups, with 48 rats per group. UW, EC, LPD, or KH solution was used in each group, and the animals were further randomly divided into 6 subgroups of 8 rats each according to preservation time. Group 1 was not subjected to hypothermic storage and was used as the normal control group. In this group the left lung was immediately transferred to the perfusion chamber for function studies. In the remaining 5 groups, the lungs were preserved for 4 hours (group 2), 6 hours (group 3), 8 hours (group 4), 12 hours (group 5), and 24 hours (group 6). During the perfusion period, the isolated lung was ventilated with room air at a respiratory rate of 40 to 50 cycles/min, a tidal volume of 2.5 to 3.5 mL, and a positive end-expiratory pressure of 0.5 cm H₂O.

Procedure for lung function studies. After connecting to the perfusion apparatus, a period of 5 to 10 minutes was needed for equilibration. Pulmonary arterial blood flow, pulmonary perfusion pressure, and airway pressure (AWP) were recorded continuously on a Gould strip chart recorder. The lungs were constantly inspected for edema, hemorrhage, or atelectasis. Blood samples were taken from the pulmonary artery and pulmonary vein every 10 minutes for blood gas analyses with a Nova State Profile 5 blood gas analyzer (Nova Biomedical, Waltham, Mass). From these parameters, pulmonary vascular resistance (PVR), airway resistance, static lung compliance, and pulmonary vein oxygen gain were calculated.

At the end of the experiment, lung tissue samples were taken for histologic and wet/dry weight ratio studies. For lung tissue wet-to-dry weight measurements, the samples were

blotted to remove excess water, and their wet weights were recorded. The samples were then placed in the 80°C oven for 3 days before dry weights were obtained.

Histologic study. Tissue samples were obtained from the upper lobes of the lungs. Each sample was then immersion fixed overnight at 4°C in 10% buffered formalin solution containing 1% glutaraldehyde. Four to six 1-mm cubes were cut with a sharp blade from each lung sample, postfixed in 1% osmium tetroxide, dehydrated in ascending concentrations of ethanol, and embedded in Araldite 502 fixative. After polymerization, 1- μ m thick sections were cut and stained with toluidine blue for light microscopic viewing. Thin sections were stained with uranyl acetate and lead citrate before being examined with a Philips 201C electron microscope.

Statistical analysis. Data were collected every 10 minutes during the perfusion period from 0 to 60 minutes. In each subgroup of 8 lungs, there were 56 values for each variable. These data points were collected and managed by using a commercial spreadsheet software package (Lotus 123 for Windows, version 1.0) yielding the mean, SD, and SEM for each group at each preservation time period. A commercial statistics software package (SigmaStat, version 1.01, SPSS, Inc, Chicago, Ill) was used for data analysis. The data were first evaluated by using analysis of variance for repeated measures. Significant effects were further examined by using the Dunnett procedure to compare all groups. All data were expressed as mean values $\pm$ SEM.

Results

Pulmonary perfusion flow and PVR. Normal pulmonary perfusion flow ranged from 1.88 ± 0.28 to 2.89 ± 0.29 mL/min (mean, 2.59 ± 0.11 mL/min). After 4 hours of preservation, flow decreased slightly in all groups except the LPD group. After 6 hours of preservation, flow was diminished further in each group, including the LPD group, with a continuous decline after 8 hours of preservation in the EC and KH groups. Flow in these two groups decreased to less than 1 mL/min after 12 and 24 hours of preservation. However, in the UW and LPD groups, the decrease in flow was not that severe (ie, less flow than the 4-hour and 6-hour groups but higher flow than the EC and KH groups; $P = .001$). Overall, the LPD group maintained the best flow (Fig 2).

Normal PVR ranged from 9.28 ± 0.70 to 17.15 ± 3.45 mm Hg $\cdot$ mL⁻¹ $\cdot$ min⁻¹ (mean, 9.67 ± 0.26 mm Hg $\cdot$ mL⁻¹ $\cdot$ min⁻¹). PVR increased slightly at 4 hours, but this increase was only statistically significant in the KH group, in which it increased to 16.29 ± 0.21 mm Hg $\cdot$ mL⁻¹ $\cdot$ min⁻¹ ($P = .02$ compared with 0 hours). PVR increased significantly after 8 to 12 hours of preservation. This increase was especially significant in the EC and KH groups but less severe in the LPD group at almost all time periods (Fig 3).

Fig 2. Comparison of pulmonary blood flow in isolated rat lungs.

Fig 3. Comparison of PVR in the 4 groups during perfusion.

Maximum AWP and static lung compliance.

Maximum AWP in the normal control animals ranged from 7.50 ± 0.59 to 10.13 ± 1.19 mm Hg (mean, 8.55 ± 0.34 mm Hg). Maximum AWP increased significantly after 4 hours of preservation, especially in the UW and KH groups, in which it almost doubled ($P = .005$ compared with 0 hours) and continued to increase. The LPD group had the smallest increase in AWP during all time periods, except at 24 hours (Fig 4). Maximum airway resistance exhibited similar changes.

Static lung compliance in the normal control animals ranged from 0.22 ± 0.02 to 0.28 ± 0.02 mL/mm Hg (mean, 0.25 ± 0.01 mL/mm Hg) and decreased gradu-

ally during the preservation period. This decrease was most significant in the UW and KH groups at 4 and 6 hours ($P = .02$ compared with 0 hours). After that, the decrease was not as significant. In the LPD group the decrease in static lung compliance was much slower. The decrease in the EC group stayed between these two extremes (Fig 5).

Oxygen exchange capacity. Pulmonary venous oxygen gain in the normal control animals ranged from 78 ± 15 to 132 ± 15 mm Hg (mean, 121 ± 6 mm Hg). Oxygen gain decreased sharply in the UW and KH groups after 4 hours of preservation. In the EC and LPD groups it was maintained at almost normal levels.

Fig 4. Comparison of maximum AWP of the isolated lungs in the 4 groups.

Fig 5. Comparison of static lung compliance in the 4 groups.

However, it decreased in all groups after 6 hours of preservation ($P = .005$ compared with normal levels). It decreased further after 8 to 12 hours of preservation, but the decrease was not as sharp as that seen at the beginning. All groups showed very low oxygen gain at 24 hours of preservation (Fig 6).

Lung tissue wet/dry weight ratio. Average normal lung tissue wet/dry weight ratio was 6.23 ± 0.33 . It increased gradually during the preservation period in all groups except the UW group. The increase was most dramatic in the KH group. The UW group maintained a low ratio. Even after 24 hours, it was only slightly higher than normal (Fig 7).

Electron microscope study. The normal control ani-

mals taken at 0 hours showed a typical lung parenchyma with numerous clusters of alveoli. The interalveolar wall was lined by flattened type I pneumocytes and a few bulging type II pneumocytes on the respiratory surface. The vascular surface was continuously paved by thin-walled endothelial cells. The interstitium contained either a single fused or two distinct basal laminae, some reticular fibrils, and occasionally fibroblast-like cells. The perfusion process removed most of the erythrocytes, but a few adhering leukocytes and alveolar macrophages remained (Fig 8). Early ultrastructural changes appeared similar among these groups. In the 4- and 6-hour samples taken from the EC or UW groups, little cytologic change was observed. Signs of

Fig 6. Comparison of pulmonary venous oxygen gains in the 4 groups during perfusion.

Fig 7. Comparison of lung tissue wet/dry weight ratios after preservation and perfusion.

deterioration, such as the increased heterochromatin formation in pneumocytes and endothelial cells, became common by 12 hours of hypothermic preservation (Fig 9). Although the tissue remained intact, by 24 hours the majority of the cells showed some degree of mitochondrial swelling and vesiculation of the rough endoplasmic reticula. Many nuclei contained highly compacted chromatin. The endothelial cells continued to exhibit hyperchromatic cytoplasm, with a plethora of microvilli formation (Fig 10). However, samples from the lungs preserved with LPD solution appeared slightly better. The endothelial lining showed small bleb formation but no other changes. The intact type II pneu-

mocyte contained lamellar bodies, a few vesiculated rough endoplasmic reticulum, and intact mitochondria (Fig 11). The worst samples were seen from the lungs preserved with KH solution. Changes were observed in both the pneumocyte and the endothelium. In the former, heterochromatin often predominated and the mitochondria appeared more compact and darkly stained. Hyperchromatic nuclei and the darkly stained cytoplasm were associated with the endothelium (Fig 12). Although no quantitative electron microscopy was performed, the inferior tissue preservation in the last group was distinctive even at light microscopy level. Ultrastructural changes in both the EC and UW groups

Fig 8. A portion of normal control lung tissue showing the presence of a type II pneumocyte with a lamellar body (arrows) and a few scattered mitochondria (*M*). The associated capillary (*C*) is lined by a thin rim of endothelium with a patent lumen (original magnification 28,000 $\times$).

Fig 10. A section taken from a 24-hour EC solution-preserved lung showing a type II pneumocyte with swollen mitochondria (*M*) and vesicle formation (*V*). The endothelial surface is lined by a plethora of microvilli (arrows; original magnification 28,000 $\times$).

Fig 9. A well-preserved type II pneumocyte in a lung preserved in a 12-hour UW solution is contrasted by darkly stained endothelial cells with microvilli projections (arrowheads; original magnification 9000 $\times$). *C*, Capillary; *M*, mitochondria.

Fig 11. A section of rat lung preserved for 24 hours with LPD solution. Except for the nuclear chromatin becoming more condensed, the lung parenchyma appeared intact and within normal range. Note the presence of a type II pneumocyte with a darkly stained nucleus (original magnification 8500 $\times$).

appeared similar at 24 hours, and changes in these two groups were somewhere between those found in the KH and LPD groups.

Pattern of functional recovery during reperfusion.

At the beginning of reperfusion, lung function appeared to be similar among different subgroups. This is especially true for the first 10 to 20 minutes of reperfusion, when all the lines tend to be very close. Only after 20 to 30 minutes of perfusion did they show more differences. One example is airway resistance (Fig 13), in which more differences were shown after 30 minutes of reperfusion.

Discussion

Among the 4 solutions used in this study, LPD appeared to have the best overall protection to lung function, with higher pulmonary arterial flow and static lung compliance and lower PVR and AWP. However, UW solution appears to be the most effective in preventing tissue edema. This has been attributed to more impermeant contents in UW solution. The benefit of these agents in suppressing cell swelling has been shown not only in lung-preservation solutions but also in other organ-preservation solutions.^{9,10} Unfortunately, less tissue edema does not necessarily translate

Fig 12. Nuclear chromatin condensation in a type II pneumocyte and the adjacent endothelial cells (*E*) indicate a relatively poor tissue preservation with KH solution alone for 24 hours (original magnification 13,000 $\times$).

into better function directly. UW solution caused higher AWP and lower compliance. One contributing factor may be that the higher potassium concentrations in UW solution may cause vascular endothelial damage¹¹ and pulmonary vasoconstriction, resulting in an uneven distribution.^{2,9} Impaired flow in the microcirculation after reperfusion is a potential problem after lung transplantation.¹² The higher viscosity in UW solution makes this situation worse. The use of modified low-potassium UW or EC solutions (potassium concentration of only 4-20 mmol/L) for lung preservation has been reported to improve results.^{4,13} The use of pulmonary vasodilators, such as epoprostenol (prostacyclin; prostaglandin I_2) and alprostadil (prostaglandin), has also been reported to effectively extend preservation of the lung.¹⁴ Such intervention was not used in this study to allow the direct comparison of flush solutions, and the use of these vasodilators is not universally accepted.¹⁵⁻¹⁷ It is interesting to note that both UW and EC solutions had a similar effect, but EC solution tended to have a more uniform protection than UW solution in short-term preservation (4-6 hours). Only after 8 hours did UW solution show better function than EC solution, as indicated by pulmonary arterial flow, PVR, AWP, and oxygen exchange capacity. This finding is in agreement with those of other studies. In a study reported by Bresticker and colleagues,⁵ EC solution showed worse lung function than UW solution after 17 hours of preservation. In cultured pulmonary endothelial cells, Hall and colleagues¹⁸ found that EC solution provided a faster structural and functional recovery than UW solution. However, Carbognani and colleagues¹⁹ did not find any significant difference between these two

solutions at 6 hours of preservation. Our results may provide some clue to many conflicting reports. It appears that there is a switch time during which these two solutions provide similar results, and this time is around 6 to 8 hours.

In contrast to the UW and EC solutions, flushing with LPD solution produced very little increase in PVR and an insignificant decrease in pulmonary arterial flow within 4 to 6 hours. During reperfusion, pulmonary arterial flow and pulmonary vein oxygen gain were higher, and PVR and AWP were lower in lungs flushed with LPD solution. The beneficial effect of LPD solution has been reported in lung preservation²⁰⁻²³ and in cell or tissue cultures.^{24,25} Although the exact mechanism is still not clear, several beneficial effects of dextran have been proposed. These include improving microvascular flow under various conditions²⁶; coating the surface of red blood cells, resulting in disaggregation; and increasing the deformability of red blood cells.²⁷ Further benefit may be gained from the added antithrombotic effect resulting from the surface coating of platelets and endothelial cells²⁸ and reduced lipid peroxidation.²⁹ Dextran is impermeable to cell membranes and may counteract the obligatory cell swelling caused by anoxic hypothermic storage.²² Although we do not know which property is the most important, it appears that a combined role of these effects is important.

Our results also indicate that a short perfusion time may not correctly reflect lung function because during the first 10 to 20 minutes of perfusion, all the lines tend to be very close. This phenomenon was also shown in some previous studies, such as those by Hausen,²³ Xiong,³⁰ Hopkinson,³¹ Bresticker,⁵ and their colleagues. We still do not know the exact mechanism for this phenomenon, but caution must be taken when a very short perfusion time is used for lung function tests.

Although a complete detailed comparison is beyond the scope of this article, ultrastructural findings indicate that regardless of the solutions used, there is a gradual morphologic deterioration with preservation time. The differences among the 4 groups are very slight at earlier stages (4-8 hours) and are better shown at later stages. Although there is a clear morphologic advantage with the use of UW, EC, or LPD solutions over KH solution, the combined morphologic data and the physiologic records would favor the use of LPD solution.

Although KH solution has low potassium concentration like LPD, its protective effect is clearly least among the 4 solutions tested. This fact shows that

Fig 13. The change of airway resistance (AWR) during a 60-minute perfusion period in rat lungs preserved in UW solution. Note that during the first 10 to 20 minutes, all the values tend to be much closer than those after 30 minutes of perfusion.

extensive research work in the past 3 decades has produced some encouraging results. It also proves that further refinement of the pulmonary preservation solutions that provide better function and morphologic protection is possible.

Although this study has provided the most complete time-related results combined with ultrastructural studies, there are still several limitations.

First, because small animals have a much higher metabolic rate³² and rodent lungs have a higher sensitivity to potassium concentrations, extrapolation to larger animals or human subjects may be more difficult. This may explain some of the differences between the findings of our study and those of some other studies.^{33,34}

Second, in clinical practice many centers use pulmonary vasodilators, such as prostacyclin or prostaglandins. This may compensate for some of the adverse effects caused by higher potassium in UW and EC solutions, therefore altering the final results.

Third, unlike the heart, liver, and kidney, the best preservation temperature for the lungs may not be at 0°C to 4°C.³⁵ This is another issue that needs further study.

Nevertheless, the results showed consistent changes of lung function with hypothermic preservation time, indicating a very stable model for isolated lung function tests. The results provide a useful guideline for improving solutions for maximum lung preservation.

In conclusion, rat lung function is impaired gradually during hypothermic preservation at 4°C. However, many lungs still maintain good function after 6 hours of preservation. When the preservation time exceeds 12

hours, lung function is severely impaired. It appears that LPD solution provides the best overall protection among the 4 solutions tested. In short-term (4-6 hours) hypothermic preservation, LPD and EC solutions provide more uniform protection than UW solution. However, lungs preserved by UW solution had the least tissue edema.

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