

The Optimum Colloid Osmotic Pressure for Lung Preservation

—A hyperoncotic solution which contains a high concentration of hydroxyethyl starch (HES) prevents pulmonary edema during preservation and reperfusion periods in hypothermic canine lung preservation—

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The optimum hydroxyethyl starch (HES) concentration and colloid osmotic (oncotic) pressure were determined for lung preservation. The lungs of twenty-five mongrel dogs were isolated and flushed with one of four different solutions and stored at 4-6 °C for 24 hours. The lungs of each group were flushed and cold-stored as follows: Group 1 with Modified-Collins (CM) solution (n=6); Group 2, CM + 3 % HES (n=6); Group 3, CM + 6 % HES (n=8); Group 4, CM + 9 % HES (n=5). After the hypothermic period, the isolated left lung was reperfused for 120 min.

During reperfusion, the airway pressure (AWP) in Group 4 was significantly lower than in Groups 1 or 3. Static lung compliance (Cst) in Groups 2 and 4 was apparently higher than that in Group 1. Pulmonary vascular resistance (PVR) in Group 4 was significantly lower than in Group 1 throughout the reperfusion period.

The wet to dry ratios (W/D) before perfusion in Group 1 (6.52 ± 0.55) and in Group 2 (6.05 ± 0.74) were significantly higher than before preservation (5.19 ± 0.21). The W/Ds after reperfusion in Group 3 (6.82 ± 0.78) and Group 4 (7.04 ± 1.22) were significantly lower than that in Group 1 (9.40 ± 2.09).

In conclusion, a hyperoncotic solution which contains a high concentration of HES is useful for hypothermic canine lung preservation because it prevents pulmonary edema during both preservation and reperfusion periods.

INTRODUCTION

The University of Wisconsin (UW) solution has been found to preserve effectively *in vitro* the lungs of experimental animals¹⁾⁻⁶⁾, and has been applied widely in clinical kidney⁷⁾, pancreas⁷⁾⁸⁾ and liver⁷⁾⁹⁾ transplantation.

The UW solution contains the colloid HES (hydroxyethyl starch), which exerts colloid osmotic (oncotic) pressure and prevents interstitial edema¹⁰⁾¹¹⁾ and endothelial damage¹²⁾. Recently, however, it was reported that HES can be eliminated from the UW solution without detriment in the cold storage of kidneys and livers¹³⁾⁻²¹⁾. However, a higher concentration of oncotic agents in the flush-out and cold-storage solutions may be required to prevent fluid from entering the alveolar space²²⁾.

In the present study, the efficacy of HES was evaluated

and determined its optimum concentration for lung preservation in the isolated lung perfusion model¹⁾.

MATERIALS AND METHODS

Twenty-five adult mongrel dogs weighing 8-13 kg were anesthetized with intravenous pentobarbital (0.5 ml/kg of body weight) and intubated. The dogs were ventilated with 100 % oxygen using a Harvard ventilator set at a tidal volume of 35 ml/(kg of body weight) and a rate of 14 cycles/min. Median sternotomy was performed, 5000 units of heparin sodium was administered intravenously, and both lungs were removed en block with the heart. A poly-ethylene canula was secured in the main pulmonary artery. A 9.0 mm cuffed endotracheal tube was inserted through the trachea and ventilated with room air at the same volume and rate. The lungs were flushed with 500 ml of one of four different solutions at 4-6 °C through the main pulmonary artery. The mean PA flush pressure was monitored continuously and the flush time was recorded. Then, both lungs were inflated with room air to end-tidal volume, placed in a plastic box filled with each solution, and stored in a refrigerator at 4-6 °C for 24 hours.

The mongrel dogs were assigned to one of four groups which differed in the flush solution used. In Group 1 (n=6), lungs were flushed with modified-Collins solution (ROUSSEL MORISHITA CO., LTD. OSAKA JAPAN), in Group 2 (n=6) with Modified-Collins solution + 3 % Hydroxyethyl starch (AJINOMOTO CO., INC. TOKYO), in Group 3 (n=8) with Modified-Collins solution + 6 % Hydroxyethyl starch, and in Group 4 (n=5) with Modified-Collins solution + 9 % Hydroxyethyl starch. One mM allopurinol and 3mM glutathione, the same concentrations used in the UW solution, were added to each solution as oxygen free radical scavengers.

There was no significant difference in the concentration of potassium (85.6 ± 4.5 mmol/l) or sodium (18.4 ± 4.4 mmol/l) or pH (7.29 ± 0.06 at room temperature) among the four experimental solutions. The viscosity of each solution was 1.35 ± 0.04 cp in Group 1, 2.28 ± 0.13 cp in

Group 2, 4.30 ± 0.03 cp in Group 3, and 6.34 ± 0.05 cp in Group 4.

After a hypothermic period, the right main pulmonary artery and right main bronchus were ligated to isolate the left lung. The isolated left lung was reperfused for 120 min. An arterial canula was connected to a circuit containing a reservoir primed with fresh allogeneic blood which had been drawn from a femoral vessel and stored in citrate-phosphate-dextrose. The number of white blood cells in the perfusate was counted before and during the reperfusion period. The pulmonary vein was left open so as to allow the lung perfusion to drain freely into the reservoir. The left lung was ventilated with room air at a tidal volume of 20 ml/kg of body weight and a rate of 10 cycles/min. The perfusion was pumped continuously with a roller pump and maintained at 37 °C in a small temperature-controlled bath. A small cannula within the pulmonary artery and bronchial cannula were connected to pressure transducers and a recorder permitted continuous monitoring of pulmonary arterial pressure (PAP) and airway pressure (AWP). The flow rate was measured with a pneumotachograph. Pulmonary venous pressure was set at 0 mmHg by adjusting the height of the apex of the lungs. The pulmonary flow rate was maintained at 10 ml/kg/min. Pulmonary vascular resistance (PVR) was calculated as pulmonary arterial pressure/flow rate (mmHg/l/min), and static lung compliance (Cst, effective lung compliance) as flow rate/pressure (ml/cmH₂O), at 1.2 seconds into the end-inspiratory plateau. Blood gas analysis of the pulmonary venous perfusate was performed. Lungs were weighed before perfusion (after preservation for 24 hours) and after reperfusion. Then, the lungs were placed in a desiccator at 160 °C for 48 hours after which they were again weighed. The wet to dry ratio (W/D) was calculated as the wet lung weight divided by the dry lung weight.

The data were compared among the groups using the unpaired -Wilcoxon test. Any p-value of less than 0.05 was considered significant.

RESULTS

The white blood cell count in every group decreased significantly after several minutes of reperfusion and remained at the same level throughout the reperfusion period. The PaO₂ did not differ significantly among the four groups. Mean pulmonary flush pressures (MFP) and flush times in each group are shown in Table 1. The MFP in Group 2 was significantly higher than in Group 1. There was no significant difference in MFP between Groups 3 and 4, and Group 3 had a significantly higher MFP than did Group 1 ($p < 0.05$) or Group 2 ($p < 0.01$). The MFP in Group 4 was significantly higher than that in Group 1. The flush time in Group 2 was significantly longer than in

Table 1. Pulmonary Flush Parameters (mean \pm SD)

Mean Pulmonary flush pressure (MFP) increases as the HES concentration rises, however there was no significant difference in MFP between groups 3 and 4. Flush time increased as the HES concentration rose.

	Mean Flush Pressure(MFP) (mmHg)	Flush Time (min)
CM (group 1)	3.67 \pm 0.68	18.0 \pm 3.5
CM+HES3% (group 2)	4.92 \pm 1.11	26.5 \pm 3.6
CM+HES6% (group 3)	6.80 \pm 0.91	35.3 \pm 6.5
CM+HES9% (group 4)	5.88 \pm 1.52	53.7 \pm 7.0

group 1 vs 2] $p < 0.05$ group 1 vs 2,3,4] $p < 0.01$
 group 1 vs 3] $p < 0.05$ group 2 vs 3,4] $p < 0.01$
 group 1 vs 4] $p < 0.01$ group 3 vs 4] $p < 0.01$
 group 2 vs 3] $p < 0.01$

Footnotes

CM: Modified-Collins solution

HES: Hydroxyethyl Starch

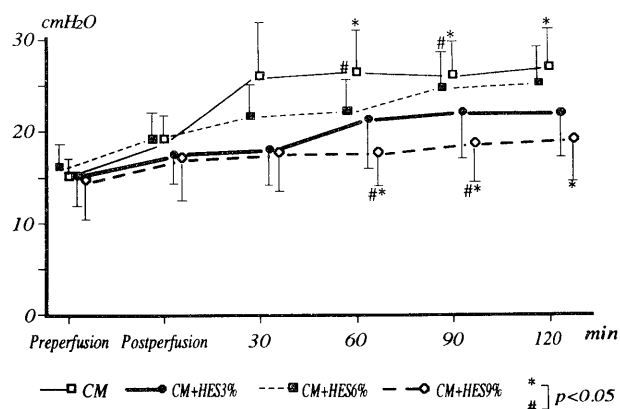


Fig 1. Airway Pressure (AWP) during Reperfusion

The AWP in group 4 was significantly lower than in group 1 or 3 after 60, 90, and 120 min of reperfusion.

Group 1, and that in Group 3 was also significantly longer than in Group 2. The flush time in Group 4 was 53.7 ± 7.0 min, which was significantly longer than in the other three groups (vs Groups 1, 2, 3; $p < 0.01$). The flush times in the four groups increased as the HES concentration was increased.

The airway pressures (AWP) in each group are shown in Fig.1. The AWP in Group 4 was significantly lower than in Group 1 or 3 after 60, 90 and 120 min of reperfusion ($p < 0.05$), and was lower, but not significantly, than in Group 2 after 60, 90 and 120 min. Static lung compliance (Cst) in every group decreased gradually (Fig.2). In Groups 2 and 4, however, it was apparently higher than that in Group 1, after 90 and 120 min of reperfusion ($p < 0.05$). In Group 3, it was insignificantly lower than in

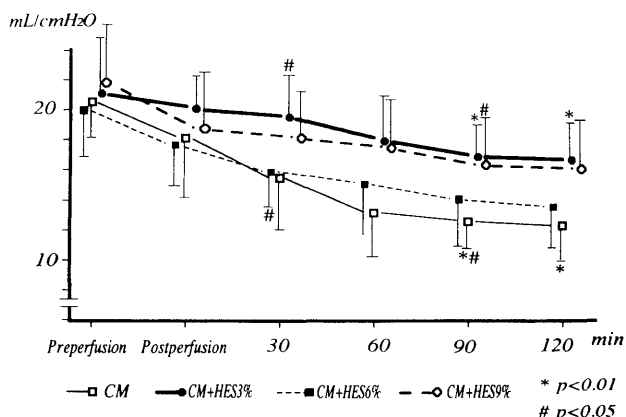


Fig 2. Static Lung Compliance (Cst) during Reperfusion
Cst in every group decreased gradually. In groups 2 and 4, it was significantly higher than that in group 1, after 90 and 120 min of reperfusion.

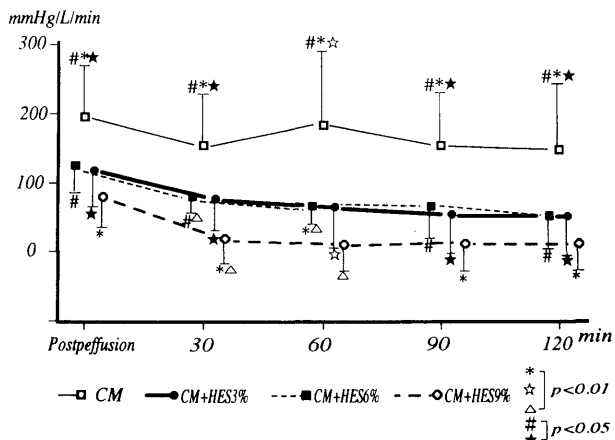


Fig 3. Pulmonary Vascular Resistance (PVR) during Reperfusion
The PVR in group 4 was significantly lower than in group 1 throughout the reperfusion periods. The PVR in groups 2 and 3 were also lower than that in group 1.

Groups 2 and 4 after 30, 60, 90, and 120 min. The change in pulmonary vascular resistance (PVR) for each group is shown in Fig.3. The PVR in Group 4 was significantly lower than in Group 1 throughout the reperfusion period (after 0, 30, 60, 90, and 120 min; $p < 0.01$), and was insignificantly lower than that in Groups 2 and 3. The PVR in Groups 2 and 3 was lower than that in Group 1 (Group 2 vs 1; after 0, 30, 90 and 120 min, $p < 0.05$; and after 60 min, $p < 0.01$; Group 3 vs 1; $p < 0.05$). The wet to dry ratio (W/D) before perfusion (after preservation for 24 hours) in each group is shown in Fig.4. Before preservation (just after harvest), the W/D was 5.19 ± 0.21 . Before perfusion in Group 1 (6.52 ± 0.55) and Group 2 (6.05 ± 0.74), the W/Ds were significantly higher than that before preservation (Group 1, $p < 0.01$; Group 2, $p < 0.05$). The

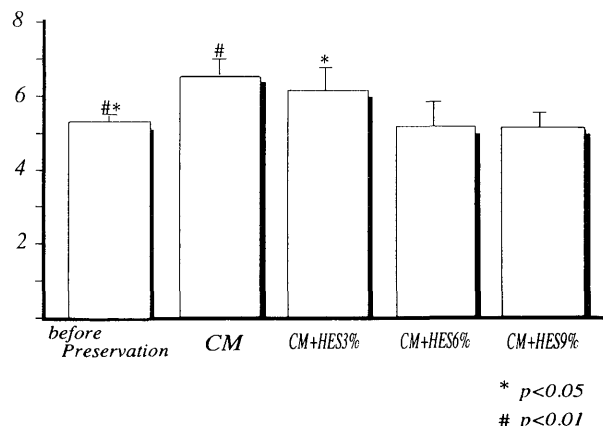


Fig 4. Wet to Dry Ratio before perfusion
The W/Ds in groups 1 and 2 were significantly higher than that before preservation. The W/D in groups 3 and 4 did not differ from that before preservation.

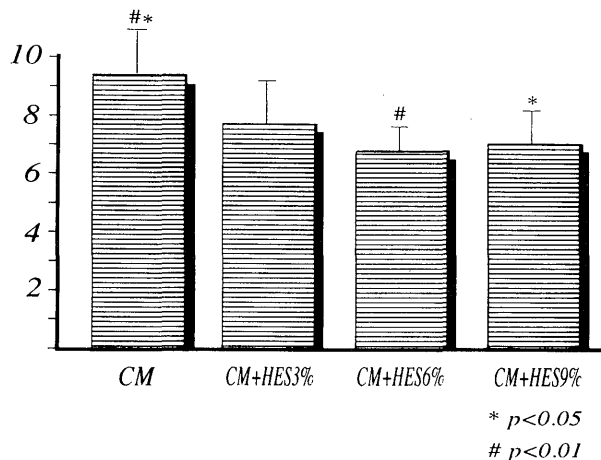


Fig 5. Wet to Dry Ratio (Postperfusion)
The W/Ds in groups 3 and 4 were significantly lower than that in group 1. There was no significant difference in W/D between groups 3 and 4.

W/Ds of Group 3 (5.13 ± 0.79) and Group 4 (5.08 ± 0.31) was significantly lower than in Group 1 (vs Group 3, $p < 0.01$; vs Group 4, $p < 0.01$) and Group 2 (vs Group 3, $p < 0.05$; vs Group 4, $p < 0.01$) and did not differ significantly from that before preservation.

After reperfusion, the W/D in Group 3 (6.82 ± 0.78) was significantly ($p < 0.01$) lower than that in Group 1 (9.40 ± 2.09) and did not differ apparently from Group 2 (7.73 ± 1.42). After reperfusion the W/D in Group 4 was 7.04 ± 1.22 , and was obviously lower than in Group 1 ($p < 0.05$). This W/D was insignificantly lower than in Group 2 and did not differ apparently from that in Group 3.

DISCUSSION

We reported previously that the University of Wisconsin (UW) solution is useful for hypothermic canine lung preservation in an isolated lung perfusion model¹⁾. The purpose of the present study is to determine the efficacy of HES, which is contained in the UW solution, and to determine its optimum concentration and colloid osmotic (oncotic) pressure in a lung preservation solution using the same model.

The UW solution, which has been applied widely in clinical kidney⁷⁾, pancreas⁷⁾⁸⁾, and liver⁷⁾⁹⁾ transplantation, contains a number of important components. Lactobionate is an impermeable anion with a large molecular mass which can prevent cell swelling. Glutathione is necessary for hypothermic preservation and reperfusion of kidney and liver²⁰⁾ because it preserves the ability of the cells to regenerate ATP and maintain their membrane integrity. Allopurinol is an inhibitor of xanthine oxidase which has been used to reduce reperfusion injury in grafts subjected to prolonged storage by diminishing free radical generation²⁰⁾.

Recently, it was reported that the use of the colloid HES (hydroxyethyl starch) was questioned and it was proposed that HES could be eliminated from the UW solution without any detriment to cold storage of the kidney and liver¹⁹⁾⁻²¹⁾.

It is hypothesized that the colloid osmotic pressure (COP) exerted by HES prevents interstitial edema and endothelial damage in lung preservation during cold storage. The oncotic pressure exerted by the colloid prevents leakage of fluid into the interstitial space by counteracting the intravascular pressure. Another beneficial effect of a colloid may be to protect endothelial structure and prevent directly hypothermia induced cell swelling¹¹⁾.

HES (Hydroxyethyl starch) is derived from amylopectin, a branched polysaccharide polymer substituted with hydroxyethyl groups at carbons 2, 3, and 6 of the glucose ring by reaction with ethylene oxide²⁴⁾. HES may have a smaller effect on coagulation and carry a lower risk of inducing an anaphylactic reaction than any other synthetic colloids, such as dextran, and has been used safely to expand volume²⁵⁾.

The movement of fluid across the endothelium is governed by "Starling's equation:

$$Q = K [(P_c - P_i) - P(COP_p - COP_i)]$$

where Q is the net flow out of capillary, K is the filtration coefficient, P_c and P_i are the hydrostatic pressures in the capillary and interstitial space, respectively, COP_p and COP_i are the corresponding colloid osmotic pressures, and P is the reflection coefficient²⁶⁾. Some studies have shown that the mean plasma colloid osmotic pressure (COP_p) of healthy volunteers varies from 19.1 to 27.8 mmHg²⁷⁾²⁸⁾. The critical minimum COP_p is 15-20 mmHg, below which pulmonary edema will occur²⁹⁾³⁰⁾. During ex vivo lung

preservation, pulmonary edema will also occur, if the COP in the alveolar capillary becomes lower than that in the interstitial space.

Arita and associates reported that the Modified-Collins-HES solution is a useful initial "wash-out solution" for preserving the pancreas, liver or kidney¹²⁾. This solution contains 6% HES, which creates a colloid osmotic pressure of 23.9 mmHg. The COP of this solution nearly equals that of normal plasma and prevents interstitial edema during the preservation period. We believe that colloid isotonic or colloid hypertonic (hyperoncotic) preservation solutions are more effective for lung preservation because they prevent pulmonary edema during the flushing and preservation periods. This study was undertaken to determine the efficacy of HES and to determine its optimum concentration and colloid osmotic pressure in a lung preservation solution.

In the present study, the W/D before perfusion (after preservation for 24 hours) in Groups 1 and 2 were significantly higher than that before preservation. During preservation, pulmonary edema may have occurred in Groups 1 and 2. The COP of both solutions were thought to be below the normal plasma colloid osmotic pressure. The W/D before perfusion in Groups 3 and 4 were the same as that before preservation. We feared that the lung weight might be decreased as a result of hypovolemia during preservation in the colloid hypertonic (hyperoncotic) solution, but significant weight loss was not found in Group 4. It is suggested that colloid isotonic and hypertonic preservation solutions are advantageous because they prevent pulmonary edema during the preservation period.

MFP increases and flush time is prolonged as the HES concentration rises. This may be a result of the increased viscosity of the solution, which contains a high concentration of HES. In this study, the viscosity of each solution correlated well with the concentration of HES (R=0.9849). Oka and associates described a similar phenomenon using the UW solution²⁾, which contains 5% HES. High pressures and long flush times are common problems encountered with hyperoncotic solutions. However, the peak flushing pressure in Group 4 was 7 to 8 mmHg and was not high enough to damage the alveolar capillary membrane or endothelium. Therefore, we do not regard as serious the flushing pressure problem. Moreover, colloid hypertonic (hyperoncotic) preservation solution may wash out RBCs with less volume than do other solutions. Adequate RBC washout during the initial cooling flush has been suggested to be a determinant of preservation solution efficacy³¹⁾.

In the present study, airway pressure was not elevated and static lung compliance did not decrease in lungs stored in a hyperoncotic preservation solution (Group 4). In contrast, airway pressure was elevated and static lung compliance decreased in lungs stored using HES-free

solutions (Group 1). From the AWP and Cst parameters, the solutions containing HES were thought to be useful even though their optimum HES concentrations could not be determined. Pulmonary vascular resistance was lowest in Group 4 from just after the start of reperfusion. A hyperoncotic solution may preserve the structure of the intra-capillary space by keeping water in the vascular compartment and, thereby, reduce pulmonary vascular resistance during reperfusion. Dextran 40, the colloid contained in low-potassium dextran (LPD) solution, exerts potentially beneficial effect by coating endothelial surfaces and platelets³². HES may have an effect similar to dextran, in reducing vascular resistance despite there being a high potassium level in the modified-Collins solution. In human heart preservation, it is known that the UW solution distributes uniformly throughout the myocardium³³. This uniformity of distribution may be related to the property of HES that it keeps water in the intravascular compartment and, thereby, improves the microcirculation. With respect to pulmonary vascular resistance, hyperoncotic solution was found to be the most useful of the four experimental solutions.

In conclusion, the efficacy of the colloid, HES, was demonstrated and the hyperoncotic solution was found to be preferred for hypothermic canine lung preservation. The colloid isotonic and hypertonic (hyperoncotic) solutions prevented pulmonary edema for 24 hours during preservation and during the early stage of reperfusion. No significant elevation of AWP or decrease of Cst was observed and the lowest PVR was found in lungs preserved with hyperoncotic solution.

Further study is necessary to determine the most optimum HES concentration and colloid osmotic pressure for a lung preservation solution, but the optimum concentration and COP may differ in each organ and the species.

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