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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 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 in Groups 1 or 3. 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, pancreas8,9 and liver10,11 transplantation. The UW solution contains the colloid HES (hydroxyethyl starch), which exerts colloid oncotic (oncotic) pressure and prevents interstitial edema12 and endothelial damage13. Recently, however, it was reported that HES can be eliminated from the UW solution without detriment in the cold storage of kidneys and livers14,15. 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 space15.

In the present study, the efficacy of HES was evaluated and determined its optimum concentration for lung preservation in the isolated lung perfusion model16.
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/1/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 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. The AWP in group 4 was significantly lower than in group 1 or 3 after 60, 90, and 120 min of reperfusion. The AWP in group 4 was significantly lower than in group 1 or 3 after 60, 90, and 120 min of reperfusion.
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 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 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 was 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, 60 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 fours) 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 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 model. 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 kidney, pancreas, and liver 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 liver 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 generation.

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 liver.

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 countering the intravascular pressure. Another beneficial effect of a colloid may be to protect endothelial structure and prevent directly hypothermia induced cell swelling.

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 oxide. 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 volume.

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

\[ Q = K \times \left[ (P_c - P_i) - P(COP_p - COP_i) \right] \]

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 coefficient. Some studies have shown that the mean plasma colloid osmotic pressure (COP) of healthy volunteers varies from 19.1 to 27.8 mmHg. The critical minimum COP is 15-20 mmHg, below which pulmonary edema will occur. 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 kidney. 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. 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 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 efficacy.

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
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