

Liver cold preservation induce lung surfactant changes and acute lung injury in rat liver transplantation

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The severity of ALI was evaluated by lung weight/body weight ratio, lung histopathological score, serum nitric oxide (NO) and endothelin (ET)-1 levels, lung tumor necrosis factor (TNF)- α and interleukin (IL)-1 β levels. Lung surfactants (LSs) were determined by micellar electrokinetic capillary chromatography.

RESULTS: With extended donor liver cold preservation time (CPT), lung histopathological scores, serum ET-1 levels, lung weight/body weight ratio and the level of TNF- α and IL-1 β in lung were increased significantly in the 180-min group compared with the sham group (3.16 ± 0.28 vs 1.12 ± 0.21 , $P < 0.001$; 343.59 ± 53.97 vs 141.53 ± 48.48 , $P < 0.001$; 0.00687 ± 0.00037 vs 0.00557 ± 0.00056 , $P < 0.001$; 17.5 ± 3.0 vs 1.3 ± 0.3 , $P < 0.001$; 10.8 ± 2.3 vs 1.8 ± 0.4 , $P < 0.001$), but serum NO levels decreased remarkably (74.67 ± 10.01 vs 24.97 ± 3.18 , $P < 0.001$). The expression of lung phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI) and phosphatidylserine (PS) increased when CPT was < 120 min, and decreased when CPT was > 180 min (PC: 1318.89 ± 54.79 vs 1011.18 ± 59.99 , $P < 0.001$; PE: 1504.45 ± 119.96 vs 1340.80 ± 76.39 , $P = 0.0019$; PI: 201.23 ± 34.82 vs 185.88 ± 17.04 , $P = 0.2265$; PS: 300.43 ± 32.95 vs 286.55 ± 55.55 , $P = 0.5054$). All these ALI-associated indexes could be partially reversed by PDTC treatment.

CONCLUSION: Prolonged CPT could induce or inhibit the expression of LSs at the compensation or decompensation stage, and some antioxidants (e.g., PDTC) may reverse the pathological process partially.

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Key words: Liver transplantation; Acute lung injury; Organ preservation; Lung surfactants

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Abstract

AIM: To investigate the relationship between donor liver cold preservation, lung surfactant (LS) changes and acute lung injury (ALI) after liver transplantation.

METHODS: Liver transplantation models were established using male Wistar rats. Donor livers were preserved in University of Wisconsin solution at 4 °C for different lengths of time. The effect of ammonium pyroglutamate (PDTC) on ALI was also detected. All samples were harvested after 3 h reperfusion.

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INTRODUCTION

Acute lung injury (ALI) is a common complication of liver transplantation, which may develop into its severest form, acute respiratory distress syndrome (ARDS), and play a pivotal role in the death of patients post-transplantation^[1]. It has been reported that the incidence of lung complications after liver transplantation is 60%-80%; the morbidity rate of ARDS is 4.5%-18%, and the case-fatality rate is 50%-70%^[2,3]. Thus, prevention of the complications is important in reducing in-hospital mortality after liver transplantation, and investigation of the etiological factors of liver-transplantation-related ALI is therefore of great importance.

Lung surfactant (LS) is synthesized primarily by alveolar type II cells and is stored in lamellar bodies. In response to some stimuli, LS is secreted to supply the surface-active monolayer. LS is a complex mix of phospholipids, neutral lipids and proteins that lines the gas/liquid interface. LS is essential for normal breathing and the severity of ALI correlates with surfactant dysfunction and abnormalities in surfactant composition^[4].

In our clinical practice, we have observed that ALI often occurs in the patients transplanted with long-persevered donor livers. Therefore, we raised a hypothesis that prolonged donor liver cold preservation time (CPT) might induce lung damage. Therefore, we conducted the present study to investigate the change of LS in liver-transplantation-induced ALI along with changes in donor liver CPT, aiming at uncovering the association between prolonged CPT and ALI.

MATERIALS AND METHODS

Experimental design

Male Wistar rats ($n = 110$) were used as donors and recipients to establish orthotopic liver transplantation models. The rats were randomly divided into six groups ($n = 10$ in each group, $n = 10$ for donor in liver transplantation groups). Donor livers from each group were preserved in 4 °C University of Wisconsin solution respectively for 0 min (sham operation), 45 min, 90 min, 120 min, 180 min, and 180 min plus intravenous injection of ammonium pyrrolidinedithiocarbamate (PDTC) at a dosage of 100 mg/kg immediately after the onset of liver reperfusion. All recipients were sacrificed at 180 min after liver transplantation.

Animal preparation and sample collection

A total of 110 adult male Wistar rats ($272 \text{ g} \pm 31 \text{ g}$; Tongji Medical Center, Central China University of Science and Technology) were used as donors and recipients. Prior to the experiment, the rats were fasted for 12 h and allowed free access to water. Liver harvesting and liver transplantation were performed under anesthesia with intraperitoneal injection of ketamine hydrochloride (80 mg/kg) and by using the method described by Kamada *et al.*^[5] and Hori *et al.*^[6]. Protocols for animal care and experimental management were approved by the ethics committee.

Blood samples were collected from the suprahepatic vena cava to determine the serum levels of nitric oxide (NO) and endothelin (ET)-1. Body weight and lung weight were measured and part of left lower lobe of lung was fixed with polyoxymethylene for histological examination. Lung tissue (200 mg) was harvested for the extraction of lung phospholipids.

Lung histopathological assessment

Left lower lobe of lung was harvested, fixed in 10% formalin, and embedded in paraffin. Tissue sections (4 μm) were stained with hematoxylin and eosin for light microscopy, and evaluated blindly by an independent consultant pathologist. Damage to the lung tissue was graded by the pathologist on a scale of 1 (no injury) to 4 (worst), as described previously^[7].

Serum ET-1 measurement

Serum ET-1 was quantified with a radioimmunoassay kit (Radioimmunity Institute of PLA General Hospital, China) by Wizard gamma counter (PerkinElmer, United States) according to the manufacturer's recommendations.

Serum NO analysis

Serum NO was measured by an NO assay kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) according to the manufacturer's protocol. The absorbance of the reaction mixture was read at 550 nm in a BioTek ELX 808 microplate reader (Bio-Tek Instruments, Winooski, Vermont, United States).

Lung weight/body weight ratio

All recipients' body weight and lung weight were measured by electronic balance.

Measurement of tumor necrosis factor (TNF)- α and interleukin (IL)-1 β in lung by immunohistochemistry

Histological sections (4 μm) of lung were cut on a rotary microtome and stained to detect intra-graft expression of TNF- α and IL-1 β . Paraffin sections were spread on a slide, and rabbit anti-rat TNF- α , IL-1 β polyclone antibodies (diluted 1:200, Santa Cruz Biotechnology, Santa Cruz, CA, United States) were used to detect the intra-graft expression of TNF- α , IL-1 β respectively. Biotin-labeled goat anti-rabbit secondary antibody (Santa Cruz Biotechnology), horseradish-peroxidase-labeled anti-

biotin, and 3,3-diaminobenzidine were used to visualize positive expression. We counted 10 randomly chosen fields per section using a light microscope at high power ($400\times$ magnification; Leica Q550CW, Germany) and the results were expressed as absorbance units (A).

Lung phospholipid extraction

Fresh lung tissue (200 mg) was homogenized with 2 mL PBS on ice, and 1 mL tissue homogenate was dissolved in 2 mL chloroform/methanol (2:1, v/v). After thermal agitation and 30 min standing at room temperature, the solution was centrifuged at 2500 rpm at 4°C for 5 min. The supernatant was transferred to a freezing tube. The above procedures were repeated, and then all the supernatants obtained were evaporated and frozen at -80°C .

Lung phospholipid analysis

Chemicals and reagents used were of analytical reagent grade. Phospholipid standard solutions (Sigma, United States) included: phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), and phosphatidylserine (PS). Micellar electrokinetic capillary chromatography (MECC) was performed in an Agilent G1600AX Capillary Electrophoresis (Agilent, Santa Clara, CA, United States). The electrophoresis buffer for MECC was composed of 35 mmol/L sodium deoxycholate, 6 mmol/L disodium tetraborate, 10 mmol/L disodium hydrogen phosphate, and 30% 1-propanol. The buffer pH value was adjusted to 8.5 with 1 mol/L HCl. MECC was conducted at a temperature of 40°C and a voltage of 18 kV. The total length of capillary was 570 mm and the detection region was 500 mm away from the injection end. Vacuum injection was performed at 50 mbar for 5 s, and ultraviolet detection was performed at $200\text{ nm}^{[8]}$.

Statistical analysis

All data were expressed as mean \pm SEM, and analyzed with one-way ANOVA and Student's *t* test. All the statistical analyses were carried out using SPSS version 13.0. $P < 0.05$ was considered to represent statistical significance.

RESULTS

General condition of the animals

The duration of donor operation was 45.6 ± 13.8 min, the time for donor liver preparation was 20.3 ± 6.7 min, and warm ischemia was avoided. The receptor operation took 26.7 ± 5.5 min, and anhepatic phase lasted for 16.1 ± 2.5 min. No significant difference was seen in portal clamping time among groups. No animal died before sample harvest.

Lung histopathological investigation

The representative lung injuries in different groups are shown in Figure 1. Lung microscopic examination revealed alveolar, perivascular and interstitial edema, neutrophil infiltration, atelectasis, disruption of alveolar and bronchiolar epithelial cells, and local hemorrhage in severe

cases with prolonged CPT. Consistent with these histopathological observations, the lung injury scores in the 180-min group were significantly higher than those in the sham group and 45-min group (3.16 ± 0.28 vs 1.12 ± 0.21 , $P < 0.001$; 3.16 ± 0.28 vs 2.05 ± 0.24 , $P < 0.001$), and were also higher than those in PDTC group although the difference was not significant (3.16 ± 0.28 vs 2.95 ± 0.16 , $P = 0.054$).

Serum NO and ET-1 assaying

The experiment results showed that with donor liver CPT prolonged, the serum NO level in the 180-min group were significantly lower than those in the sham group and 45-min group (24.97 ± 3.18 vs 74.67 ± 10.01 , $P < 0.001$; 24.97 ± 3.18 vs 69.05 ± 2.74 , $P < 0.001$) and the decline could not be reversed by PDTC (24.97 ± 3.18 vs 7.67 ± 3.79 , $P < 0.001$; Figure 2A).

With longer liver CPT, serum ET-1 levels increased significantly in the 180-min group compared with the sham group (343.59 ± 53.97 vs 141.53 ± 48.48 , $P < 0.001$). There was a significant difference between each of the operation groups and the control group ($P < 0.05$). The expression of ET-1 was inhibited significantly by PDTC (343.59 ± 53.97 vs 217.80 ± 11.32 , $P < 0.001$; Figure 2B).

Lung weight/body weight ratio

Lung weight/body weight ratio increased with prolonged CPT. It peaked in the 180-min group compared with the sham group (0.00687 ± 0.00037 vs 0.00557 ± 0.00056 , $P < 0.001$), but greatly decreased after PDTC was used (0.00687 ± 0.00037 vs 0.00576 ± 0.00016 , $P = 0.001$; Figure 2C).

Lung TNF- α and IL-1 β measurement

Figure 3 shows a significant increase in TNF- α and IL-1 β in lung with prolonged CPT, which peaked in the 180-min group compared with the sham group (TNF- α : 17.5 ± 3.0 vs 1.3 ± 0.3 , $P < 0.001$; IL-1 β : 10.8 ± 2.3 vs 1.8 ± 0.4 , $P < 0.001$). After administration of PDTC, TNF- α and IL-1 β production was significantly attenuated (TNF- α : 17.5 ± 3.0 vs 9.8 ± 2.3 , $P < 0.001$; IL-1 β : 10.8 ± 2.3 vs 7.1 ± 2.0 , $P = 0.0012$). We suggest that the prolonged CPT induced some inflammatory factors expressed in lung.

Lung phospholipid composition determination

The area under curve (AUC) represents the composition of lung phospholipids (Figures 4 and 5). With the extension of CPT, PC levels increased significantly, reaching a maximum in the 120-min group compared with the sham group (1318.89 ± 54.79 vs 406.79 ± 56.49 , $P < 0.001$), and then declined in notably the 180-min group (1318.89 ± 54.79 vs 1011.18 ± 59.99 , $P < 0.001$). No significant difference was observed between the 180-min group and PDTC group (1011.18 ± 59.99 vs 1062.58 ± 78.49 , $P = 0.1173$).

PE changed similarly with PC, reaching a maximum in the 120-min group compared with the sham group

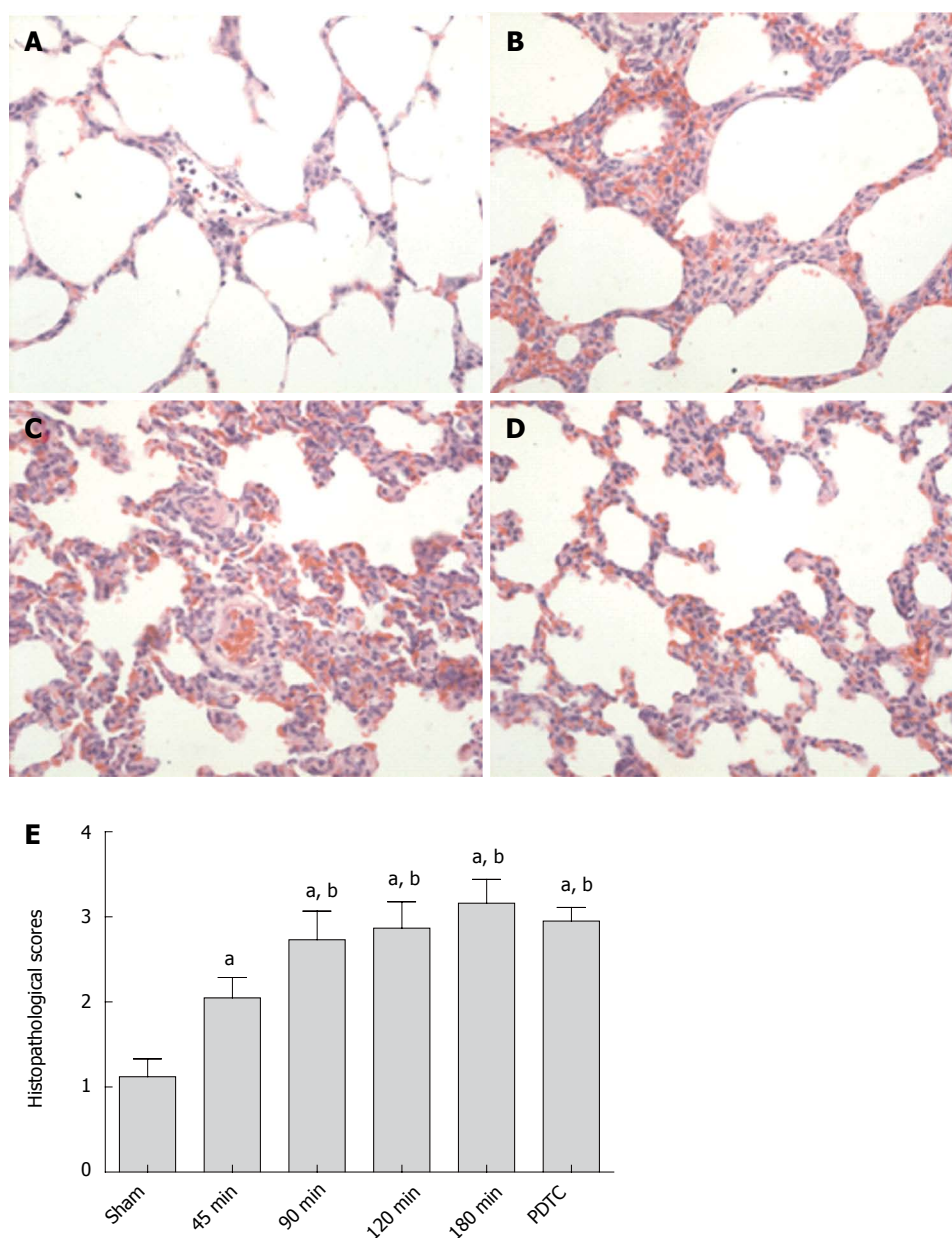


Figure 1 Representative lung tissue sections and histopathological scores. A: Sham group; B: 90-min group; C: 180-min group; D: PDTC group. Alveolar, perivascular and interstitial edema, neutrophil infiltration, atelectasis, disruption of alveolar and bronchiolar epithelial cells, and local hemorrhage aggravated with prolonged CPT; E: Lung histopathological scores in different groups. The scores in the CPT groups were significantly higher than that in the sham group, but lower than in the PDTC group. ^a*P* < 0.05 vs sham group; ^b*P* < 0.05 vs 45-min group. PDTC: Pyrrolidinedithiocarbamate; CPT: Cold preservation time.

(1504.45 ± 119.96 *vs* 430.38 ± 57.91, *P* < 0.001), and decreased significantly in the 180-min group (1504.45 ± 119.96 *vs* 1340.80 ± 76.39, *P* = 0.0019). PE in the PDTC group decreased significantly compared with the 180-min group (1340.80 ± 76.39 *vs* 1222.18 ± 100.48, *P* = 0.0082).

PI kept rising gradually, and reached a peak in the 120-min group compared with the sham group (201.23 ± 34.82 *vs* 55.12 ± 10.14, *P* < 0.001), but no significant difference was found between the 120-min, 180-min and PDTC groups (201.23 ± 34.82 *vs* 185.88 ± 17.04, *P* = 0.2265; 185.88 ± 17.04 *vs* 190.10 ± 41.75, *P* = 0.7707).

PS reached a maximum in the 120-min group compared with the sham group (300.43 ± 32.95 *vs* 51.29 ± 13.89, *P* < 0.001), and decreased in the 180-min group (300.43 ± 32.95 *vs* 286.55 ± 55.55, *P* = 0.5054), but

dropped significantly in the PDTC group (286.55 ± 55.55 *vs* 132.60 ± 40.27, *P* < 0.001).

DISCUSSION

The incidence of ALI post-liver transplantation has been reported to be 60%-80%^[3]. Despite intense research and diverse therapeutic trials, there is no effective prevention or treatment for ALI at present^[1]. Recent studies have shown that the pathogenesis of ALI involves disorders of oxidants/antioxidants, inflammation/anti-inflammation, and upregulation of inflammatory factors^[9,10]. It has been suggested that the antioxidant PDTC can inhibit some oxidants and inflammatory damage^[1].

In our study, levels of serum NO and ET-1 were used

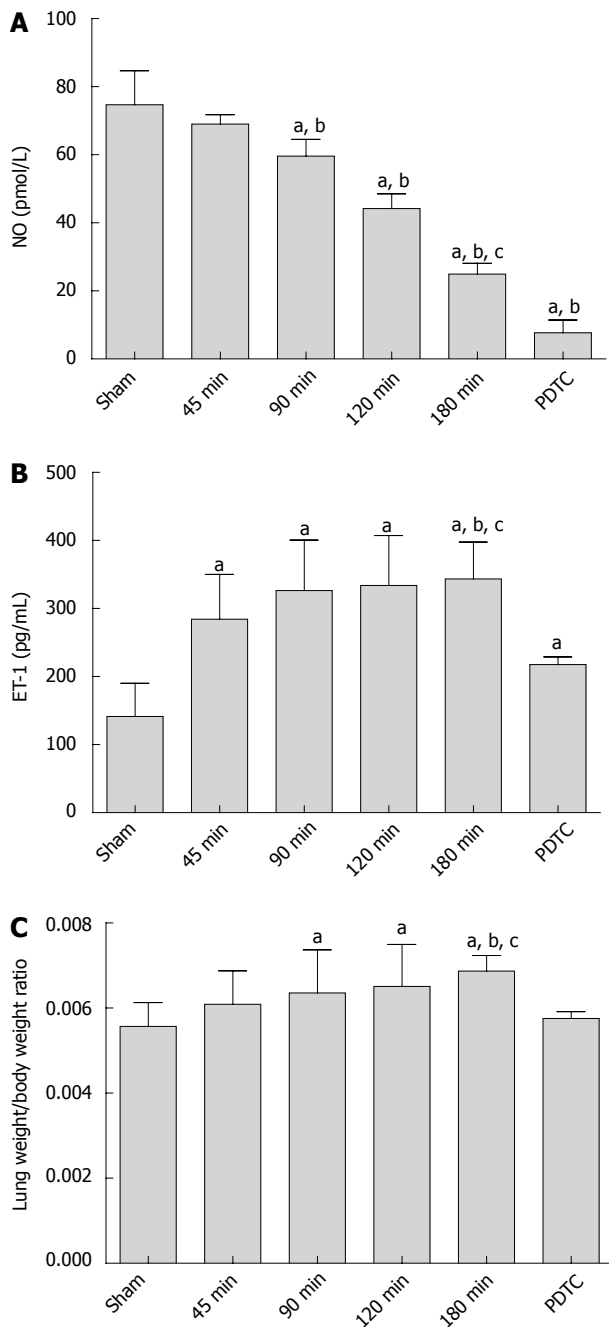


Figure 2 Serum NO, ET-1 level and lung weight/body weight ratio. A: NO levels in different groups. With CPT prolonged, NO level decreased significantly, and became even lower with PDTC injection post-reperfusion; B: ET-1 level in different groups. With CPT prolonged, ET-1 level increased significantly compared with the sham group. The PDTC group had a significantly lower ET-1 level than 180-min group; C: Lung weight/body weight ratios in different groups. The ratios increased compared with the sham group. Significant difference was observed between the 180-min group and PDTC group. ^a $P < 0.05$ vs sham group; ^b $P < 0.05$ vs 45-min group; ^c $P < 0.05$ vs PDTC group. PDTC: Pyrrolidinedithiocarbamate; CPT: Cold preservation time; NO: Nitric oxide; ET: Endothelin.

to evaluate the severity of ALI. NO and ET-1 are secreted by endothelial cells and are two important vasoactive substances that regulate mini-circulation. NO can expand blood vessels, prevent platelet aggregation, and therefore improve microcirculation. After liver transplantation, the implanted graft liberates high amounts of arginase and

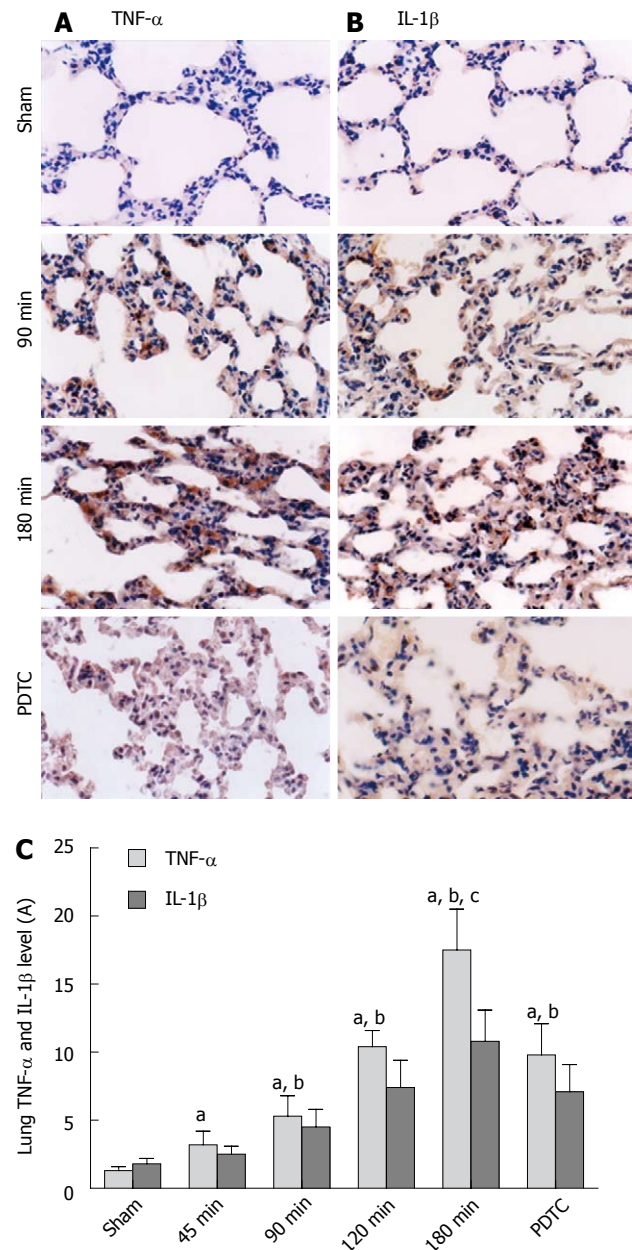


Figure 3 Immunohistochemical sections of tumor necrosis factor- α and interleukin-1 β in lung ($\times 400$). A: Immunohistochemistry sections of TNF- α with different CPT; B: Immunohistochemical staining of IL-1 β with different CPT; C: Analysis of TNF- α and IL-1 β levels. The results were expressed as absorbance unit (A). ^a $P < 0.05$ vs sham group; ^b $P < 0.05$ vs 45-min group; ^c $P < 0.05$ vs PDTC group. PDTC: Pyrrolidinedithiocarbamate; CPT: Cold preservation time; TNF: Tumor necrosis factor; IL: Interleukin.

causes L-arginine deficiency. L-arginine is the substrate of NO synthesis reaction. Its depletion influences NO synthesis after liver transplantation^[11]. This might be the reason why serum NO level drops after liver transplantation. An increase in NO level by L-arginine could attenuate LS depletion, and therefore, ameliorate postoperative pulmonary dysfunction^[12]. PDTC could inhibit cytokine-induced NO production^[13], as our study showed.

ET-1, as the most powerful vasoactive substance, can cause microcirculation disturbance and induce pulmonary injury^[14]. The slowdown of liver blood flow can concen-

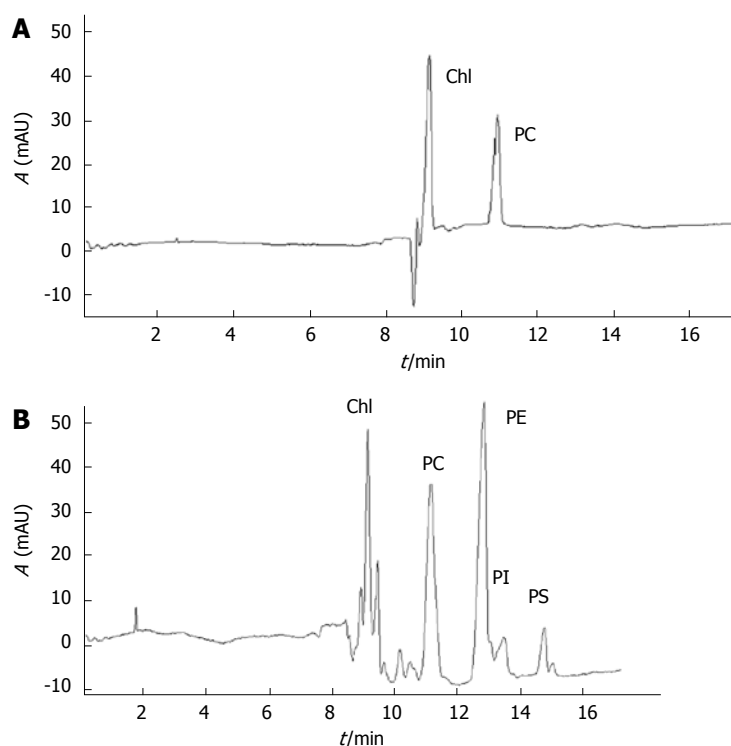


Figure 4 Pulmonary phospholipids separated by micellar electrokinetic capillary chromatography. A: Standard PC electropherogram; B: Pulmonary phospholipid extracts electropherogram. Chl: Chloroform. AUC of different chromatographic peaks represent the relative quantities of different pulmonary phospholipid components. PC: Phosphatidylcholine; AUC: Area under curve; PE: Phosphatidylethanolamine; PI: Phosphatidylinositol; PS: Phosphatidylserine.

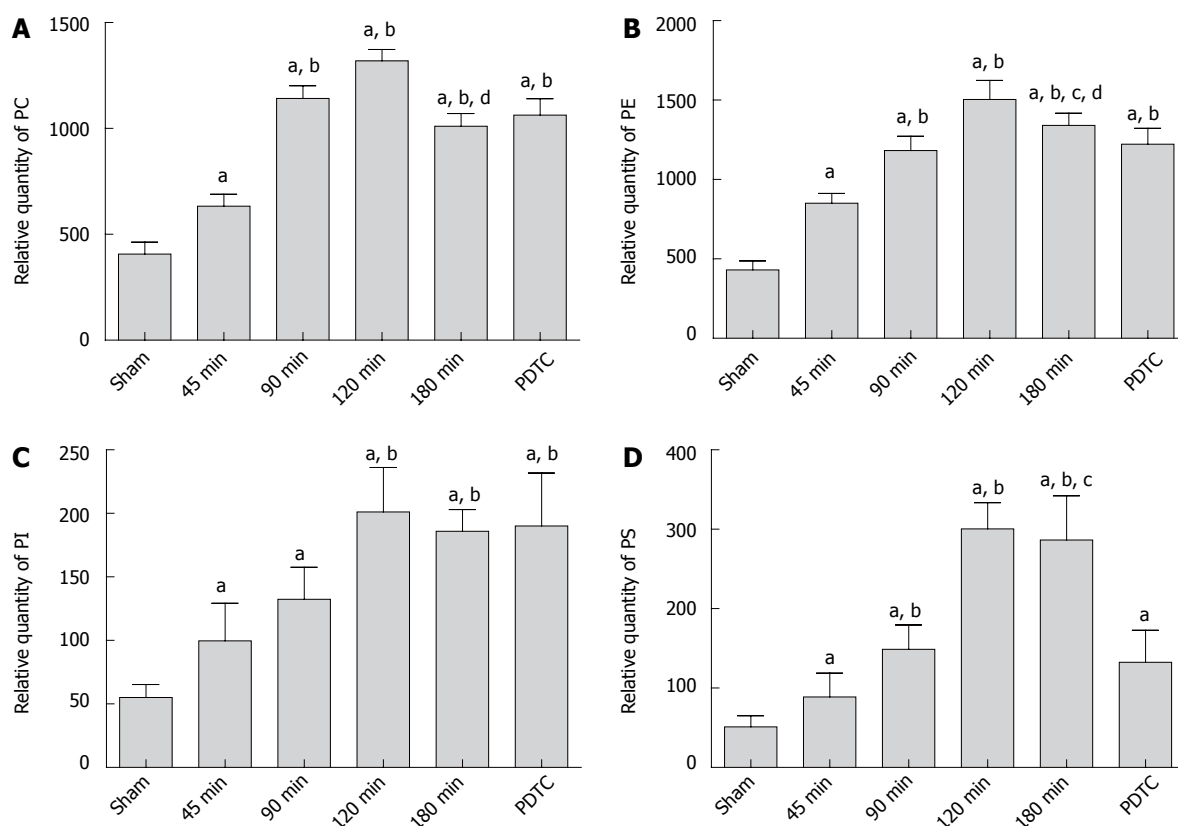


Figure 5 Relative quantities of pulmonary phospholipids. A: Relative quantity of PC; B: Relative quantity of PE; C: Relative quantity of PI; D: Relative quantity of PS. With CPT prolonged, the levels of pulmonary phospholipids increased significantly, reaching a peak in the 120-min group, and then declined in the 180-min group. The use of PDTC could inhibit the expression of PE and PS, but could not observe significant effect in PC and PI. ^a $P < 0.05$ vs sham group; ^b $P < 0.05$ vs 45-min group; ^c $P < 0.05$ vs PDTC group; ^d $P < 0.05$ vs 120-min group. PDTC: Pyrrolidinedithiocarbamate; CPT: Cold preservation time; PC: Phosphatidylcholine; PE: Phosphatidylethanolamine; PI: Phosphatidylinositol; PS: Phosphatidylserine.

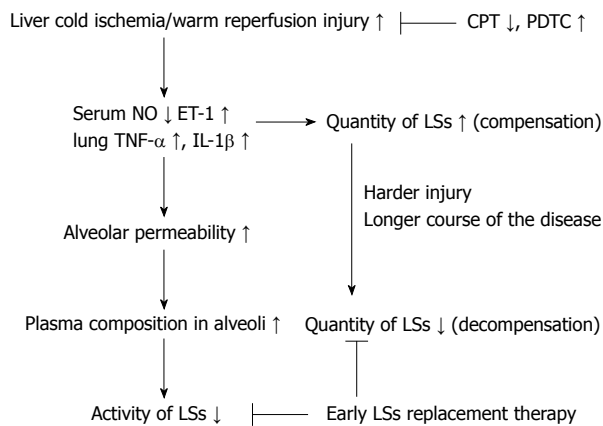


Figure 6 A schematic diagram for the mechanism of lung surfactants in liver-transplantation-related acute lung injury. With prolonged CPT of donor liver, the cold ischemia/warm reperfusion injury increased, inducing an imbalance of serum NO/ET-1 levels and production of TNF- α and IL-1 β in lungs. Consequently, alveolar permeability increased, and the plasma composition in the alveoli inactivated the lung surfactants (LSs). In the early stage of ALI, LSs increased in compensation, but in the decompensation stage, the level of LSs decreased, and ALI was aggravated. Shorter CPT or using PDTC may reduce ALI, and surfactant replacement therapy at an earlier stage may be useful in the treatment of ALI. PDTC: Pyrrolidinedithiocarbamate; CPT: Cold preservation time; TNF: Tumor necrosis factor; IL: Interleukin; ALI: Acute lung injury; NO: Nitric oxide; ET: Endothelin.

trate ET-1 in the serum and liver. We observed that the balance between NO and ET-1 was disrupted after liver transplantation.

Natural lung surfactants (LSs) are a mixture of phospholipids and specific proteins, and are produced by type II alveolar epithelial cells, stored in Golgi bodies and secreted into the alveolar space. They are important in maintaining alveolar expansion during breathing and physiological gas exchange. The pathological condition of ALI is often characterized with metabolic anomalies of LSs and disrupted lung function^[15].

We found that with prolonged CPT of donor liver, that cold ischemia/warm reperfusion injury increased. The imbalanced levels of NO and ET-1 induced capillary endothelial dysfunction. Together with TNF- α and IL-1 β produced in the lungs, the permeability of the air-blood barrier increases, just as shown by lung weight/body weight ratio and lung histopathological scores. Then, a variety of plasma compositions, such as serum, serum proteins, hemoglobin and proteases migrate into the alveolar space and inactivate LSs^[16]. At the same time, ET-1 and some inflammatory factors, such as TNF- α and IL-1 β , stimulate the production of cAMP, which can induce type II alveolar epithelial cells to secrete LSs^[17]. Because of the anti-inflammatory properties of LSs^[18], an increase in their concentration in the lungs indicates a strong compensatory ability in the defense against ALI^[19]. Our study showed that, when CPT was < 2 h, the expression of LSs increased with longer CPT, however, when CPT was 3 h, more severe injury of type II alveolar epithelial cells inhibited secretion of LSs. This agrees with the results of Shu *et al.*^[20].

In contrast, the change in LSs after ALI is time-dependent, with early increases and late decreases. Therefore, surfactant replacement therapy should be administered at an early stage of ALI, the compensation stage, to alleviate injury^[21]. If applied in the decompensation stage, the therapy may not provide satisfactory effects. This may be the reason why surfactant therapy has only limited success in ARDS^[22,23]. Furthermore, as an antioxidant, PDTC can relieve cold ischemia/warm reperfusion injury of donor liver, and partly reverse the disturbance. Thus, shortening CPT or using PDTC may be useful for alleviation of ALI post-liver transplantation. A proposed scheme of the mechanism is given in Figure 6, summarizing how LS affects liver-transplantation-associated ALI.

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COMMENTS

Background

Acute lung injury (ALI) and its severe subset acute respiratory distress syndrome (ARDS) have relatively high morbidity and mortality in post-liver transplantation patients. The pathogenesis and prevention of liver-transplantation-related ALI are not very clear. Lung surfactants (LSs) are a complicated mixture of approximately 90% lipids and 10% proteins. They are produced by type II alveolar epithelial cells and secreted into the alveolar space to maintain normal respiratory mechanics by reducing alveolar surface tension to near-zero values.

Research frontiers

Recent studies have shown that the pathogenesis of ALI involves disorders of oxidants/antioxidants, inflammation/anti-inflammation, and upregulation of inflammatory factors. Many antioxidants can inhibit some oxidants and inflammatory damage. The severity of ALI correlates with abnormalities in surfactant composition. Supplementing exogenous surfactant to newborns suffering from respiratory distress syndrome has a satisfactory therapeutic effect. Surfactant therapy has also been used in ALI/ARDS, but with only limited success.

Innovations and breakthroughs

We observed that ALI often occurred in patients transplanted with long-preserved donor livers. Therefore, we raised a hypothesis that cold preservation/warm reperfusion injury of donor liver may induce ALI after liver transplantation. To validate the hypothesis, we transplanted donor liver after different cold preservation times in rats. Prolonged cold preservation time had a positive correlation with the severity of ALI, and could induce or inhibit the expression of LSs in different time phases, and some antioxidants (e.g., ammonium pyrrolidinedithiocarbamate) may reverse the pathological process partially.

Applications

Shorter cold preservation time or some antioxidants may reduce liver-transplantation-related ALI, and surfactant replacement therapy should be useful in the early stage of ALI to achieve better results.

Terminology

Cold ischemia/warm reperfusion injury, different from warm ischemia/reperfusion injury, is a characteristic injury in organ transplantation. It depends on the length of cold storage. Liver is one of the organs that are sensitive to ischemia/reperfusion injury. Emerging evidence suggests that the early stage of the injury can be regarded as part of the immune response to injury stress and sinusoidal endothelial cells are the targets of cold ischemia, whereas hepatocytes appear to be relatively unscathed.

Peer review

This study suggests that liver transplantation in rats and the length of cold ischemia induce surfactant changes and ALI. The study was well designed and conducted.

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