AMELIORATION OF ISCHEMIC LUNG INJURY WITH PENTOXIFYLLINE

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SUMMARY

The optimum method for lung preservation in preparation for transplantation remains unresolved. In this study we evaluated the effectiveness of Pentoxifylline to find an ideal perfusate to increase the success of preservation in a model which consisted of exposing the left lung of each experimental dog to normothermic ischemia after clamping the pulmonary artery, vein and bronchus. After ischemic periods of three hours, pulmonary circulation were reestablished. The left lung of dogs was perfused with Euro-Collins solution alone in group A (n=2) and with Euro-Collins solution containing 2500 ng/ml Pentoxifylline in group B (n=2). The mean ischemic time was three hours in both groups. Specimens for light and electronmicroscopic investigations taken seven days after the initial operation, showed that addition of Pentoxifylline to the perfusate appears to be beneficial in the preservation of allograft patency in organ protection.

Key Words: Lung Transplantation, Pentoxifylline, Ischemic Lung Injury

INTRODUCTION

Lung transplantation has been applied in the management of selected patients with chronic end-stage pulmonary disease (1). The major factor limiting more widespread application of lung transplantation is a shortage of a suitable donor lung (2).

As known, ischemic and reperfusion injuries are important components of any organ transplant procedure. Calcium plays an important role in cellular events during ischemia and reperfusion (3-5). Calcium accumulation within ischemic cells followed by activation of phospholipase, synthesis of vasoactive prostaglandins and production of xantine oxidase creates further the risk of cell membrane injury.

Many investigators have tried several drugs to reduce ischemic injury during either ischemia or reperfusion (2, 6-9). The objective of the present experiment is to assess the potential benefit of pentoxifylline in preserving ischemic lungs following temporary clamping of hilae in dogs, by a method recently described by Hachida (10).

Pentoxifylline, a methylxantine with hemorrheological properties, has demonstrated benefit in preserving ischemic tissue damage associated with various vascular diseases (11-14).

MATERIALS AND METHODS

Four mongrel dogs weighing about 20-25 kg were used in this study. Each dog received endotracheal anaesthesia induced by pentobarbital and maintained by oxygen and halotane mixture following premedication by droperydole and fentanyl citrate.

A left thoracotomy was performed through the fifth intercostal space of the dog in a right lateral position. All connective tissues around the hilar structures were completely freed. The left main bronchus, pulmonary

artery and pulmonary vein were exposed and isolated. Heparin (200 units/kg) was given intravenously before the left main bronchus, pulmonary artery and vein were clamped with noncrushing clamps. Small incisions were made in the pulmonary artery and vein. A catheter was introduced into the pulmonary artery and standard Euro-collins solution (Table I) was perfused through the catheter and drained out through the incisions of the pulmonary veins.

TABLE I : MODIFIED EURO-COLLINS SOLUTION FOR PULMONARY FLUSH

Component	Concentration
K^+	115 mEq/L
Na^+	10 mEq/L
Cl^-	15 mEq/L
HCO_3^-	10 mEq/L
H_2PO_4	15 mEq/L
HPO_4^{-2}	85 mEq/L
$MgSO_4$	10 mEq/L
Glucose 50%	69 ml

In group A the left lung was perfused with 200 ml of Euro-Collins solution alone by a gravity pressure of 40 cm H_2O at initial and terminal phase of ischemia. In group B the lungs were similarly perfused but with 2500 ng/ml pentoxifylline added to Euro-Collins solution. The small incisions in the pulmonary artery and vein were closed with 6-0 prolene sutures following second perfusion and the clamps were released for reperfusion.

Thoracotomies were closed in usual manner and intercostal nerve blocks were also accomplished in all dogs. Prophylactic antibiotic regimen using mezlocillin, 1 gr/day (Baypen-Bayer) was also given while the chest tubes were in place.

Some laboratory examinations as blood counts and estimation of blood urea, creatinin, liver function test (total bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase) were also performed with induction of anaesthesia, at the initial and terminal phases of ischemia, at the end of anaesthesia and during reoperation.

Chest X-ray was taken to check the respiratory functions when needed. Figure 1 shows a normal control graphy.

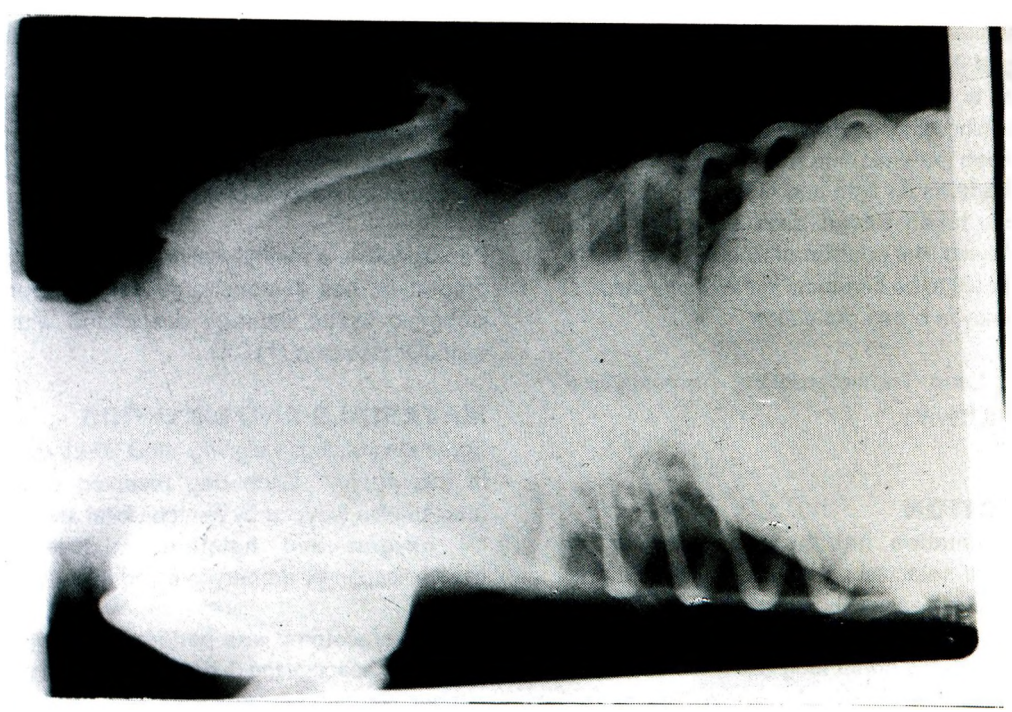

FIG.1

Light and electronmicroscopic studies were performed to all dogs. Specimens were taken from the left lower lobes during reoperation, on the seventh day after the initial operation. A biopsy was also taken from the contralateral lung as control specimen.

Specimens for light microscopic (LM) investigations were fixed in 10% formalin solution, dehyrated and embedded in paraffin. Sections were cut on a Reichert Rotary Microtome, stained with Hematoxylin-Eosin and examined with Olympus CH2 light microscope. Four slides were examined for each biopsy.

Specimens for electron microscopic (EM) investigations were fixed in 2.5% phosphate buffered glutaraldehyde and postfixed in osmium tetraoxide, dehydrated and embedded in Westopal. Sections were performed with LKB III ultramicrotome. Contrast staining was done with uranyl acetate and lead citrate and specimens were examined with a JEOL 100C electron microscope. Two grids were examined for each biopsy.

RESULTS

On operation the lung found expanded, pink in color with no pleural fluid. During the initial operation laboratory examinations revealed moderate increase in liver function values followed by a slight decrease within seven days. There was no change in renal functions either in the first operation or in the later.

Light microscopic examinations of group A revealed edema in the subpleural space and in the periphery of some arteries; disturbance of alveolar wall and disappearance of alveolar structure in some areas; presence of hemorrhage, PNL and macrophages in alveolar cavities (Fig.2). Group B showed mild subpleural edema, effusion of serous substance and presence of less PNL and macrophages in alveolar cavities (Fig.3).

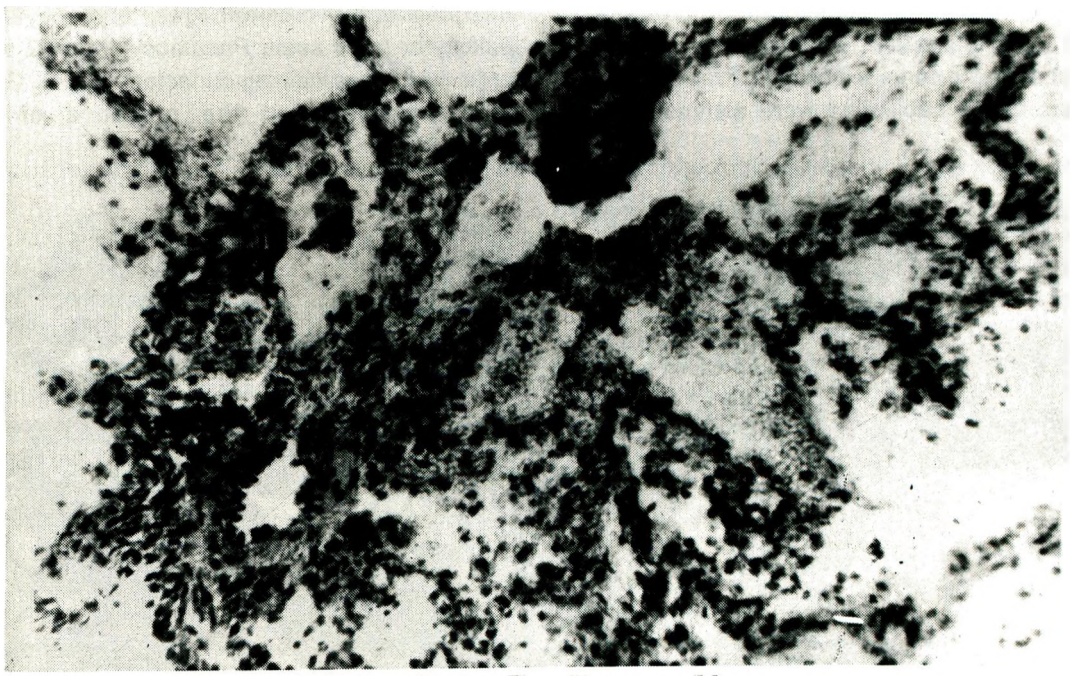

FIG.2

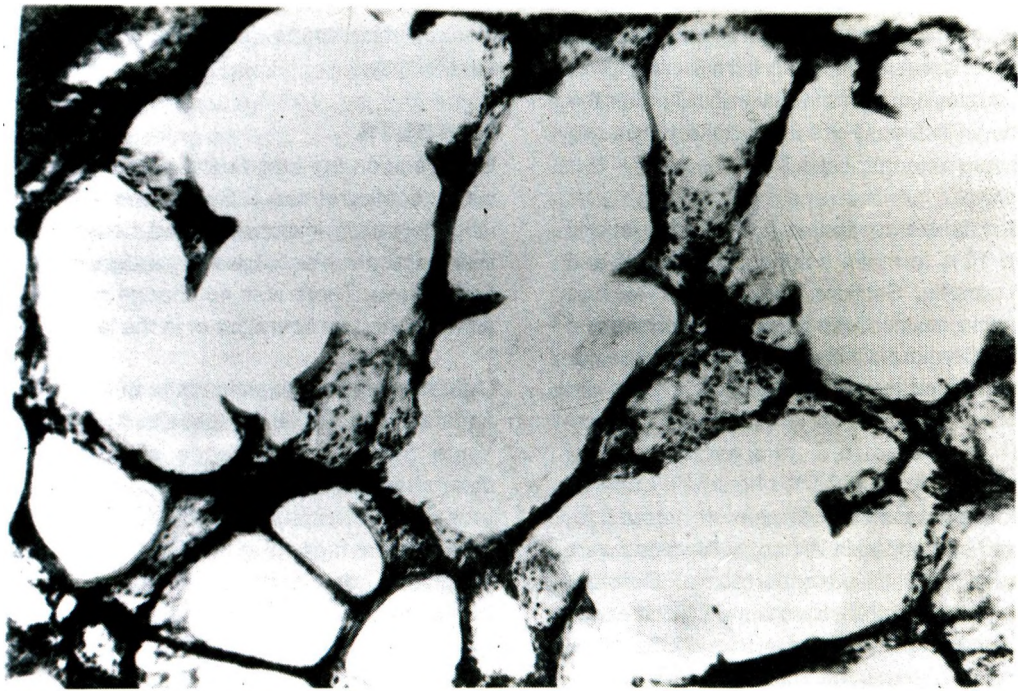

FIG.3

Electron microscopic examinations of group A disclosed cell infiltration in peribronchial and perialveolar areas. In some regions the alveolar septa were fused. Some capillaries were distended. In infiltrated areas macrophages, erythrocytes and leukocytes were seen. Pneumocyts type 2 showed large vesicles containing surfactant (Fig.4). Group B specimens revealed the presence of fibrin,

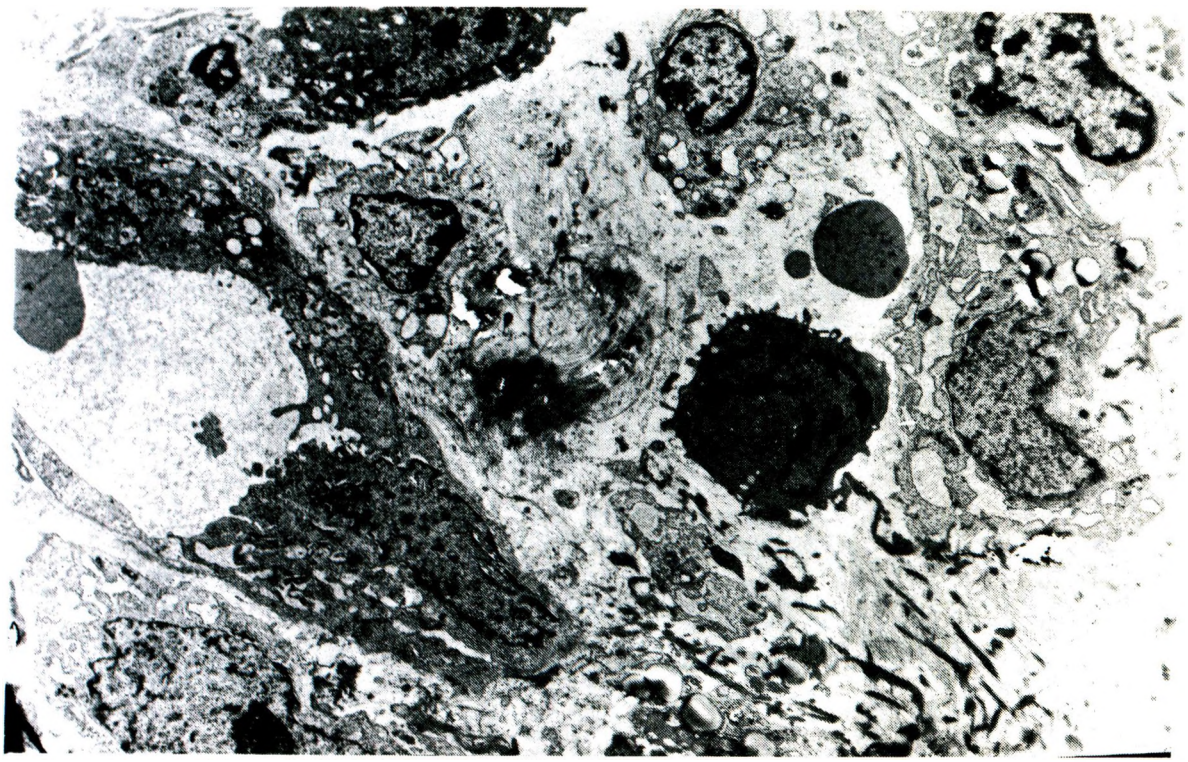

FIG.4

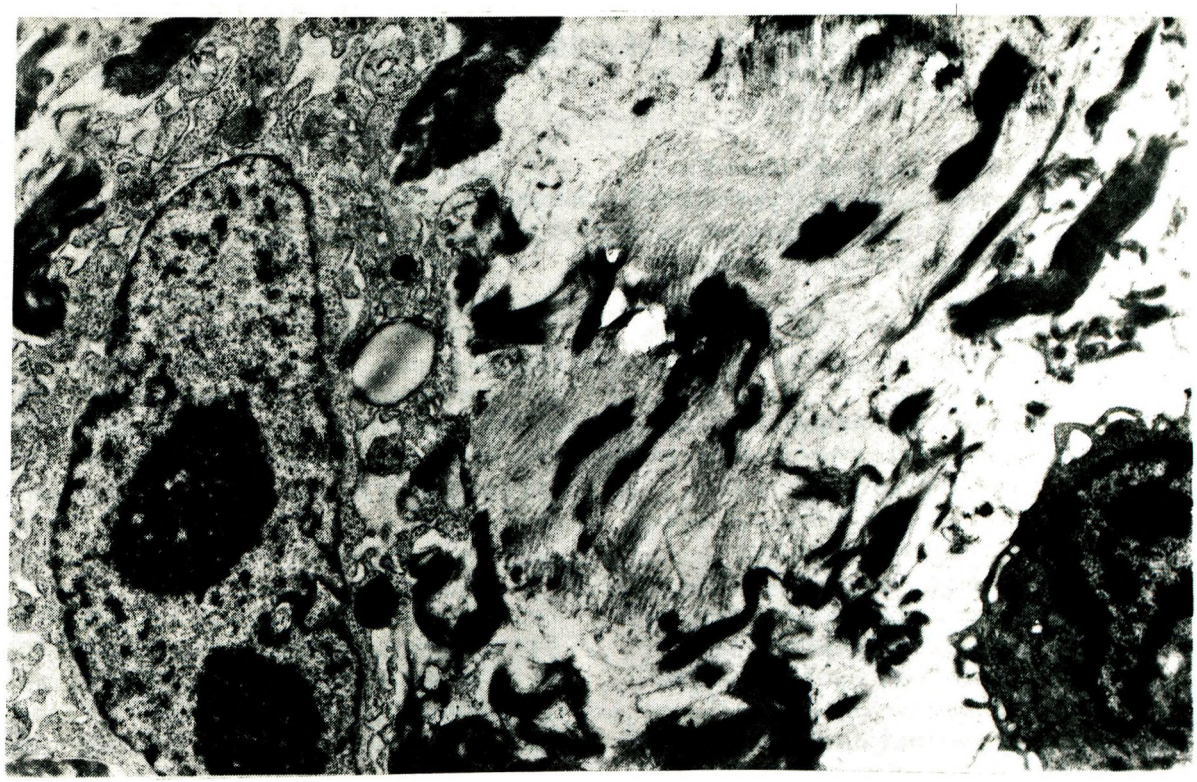

FIG.5

macrophages and blood cells in alveolar cavities (Fig.5).

DISCUSSION

The microscopic examinations support the potential benefit of pentoxifylline in lung preservation. Although both groups have some degree of alveolar exudate and interstitial edema following warm ischemia, pharmacological doses of pentoxifylline administered to lungs in group B reflected improved tolerance to brief periods of ischemia compared with group A by means of microscopic examinations. Group B lungs showed minimal congestion and mild alveolar exudate after three hours of ischemia.

Changes in the composition and temperature of the perfusate have resulted in better preservation of the lungs. Many investigators have used pharmacological agents such as calcium antagonists in preventing ischemic injury in lungs (2,7-9). Considering that all these studies have used prophylactic doses of drugs in an attempt to prevent ischemia induced damage, we have added pentoxifylline to the perfusate.

Pentoxifylline, which is a methylxantine with hemorrheological properties, has some properties in preventing ischemic tissue damage present in various vascular diseases (11-14). Pentoxifylline is associated with several hemodynamic effects, including reduction of platelet and thrombin aggregation and stimulation of vasodilatory prostaglandins (15,16). The effects of prostaglandin synthesis are somewhat confusing (17). Some investigators have demonstrated a stimulatory effect of pentoxifylline on prostacycline synthesis (16), prostacycline release following ischemia prompts vasodilation.

As conclusion, lungs perfused with pharmacological doses of pentoxifylline demonstrated significant improvement in lung preservation following a brief period of warm ischemia compared with Euro-Collins solution administered alone. The mechanism of protection remains unclear but most likely involves interaction with adenosin pathway (12). However stimulation of vasodilatory prostaglandin may also play a role in the mechanism of action. Addition of a methylxantine, such as pentoxifylline, to the perfusate appears to be beneficial in the preservation of allograft patency in organ protection (12).

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