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The preventive role of thoracic duct ligation on cerebral fat embolism in lung injury: An experimental study

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
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G Funds Collection

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Summary

Background: Cerebral fat embolism constitutes a major problem in intensive care units and treatment methods are highly controversial. Cerebral fat embolism has been thought to result from the migration of bone marrow fragments to the brain. However, the present authors observed that cerebral fat embolism is not possible unless the bone marrow particles cause alveolar wall destruction due to pulmonary artery occlusion. Thoracic duct ligation is essential for improved patient survival under such conditions. The aim was to investigate whether thoracic duct ligation plays a preventive role in cerebral fat embolism in lung injury.

Material/Methods: Pulmonary contusion was established with chest wall trauma in 20 male hybrid rabbits (n=20), with thoracic duct ligation being administered to half (n=10). Ten days after the procedure, all the rabbits were sacrificed. Brain specimens were taken using the frozen-section method, stained with Sudan Black, and examined microscopically.

Results: In the frozen brain sections the number of branches occluded by fat particles in both the central cerebral arteries was 15.5±3.02 in eight animals of the non-ligated group (GI) compared with 4.7±2.45 in two animals of the ligated group (GII). The number of occluded branches of the middle cerebral arteries was significantly higher in GI than in GII ($p<0.001$).

Conclusions: The number of branches of both central cerebral arteries occluded by lipid particles was greater in the non-ligated than in the ligated animals. It is believed that thoracic duct ligation provides significant protection against fat embolism in cases of thoracic trauma.

key words: **fat embolism • thoracic duct ligation • lung injury**

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Background

The primary function of the thoracic duct is the transportation of digestive fat to the venous system. Lymph volume and weight of flow have been estimated at 1.38 ml per kg of body weight per hour [1]. Volumes of up to 2500 ml of chyle in 24 hours have been collected from the cannulated human thoracic duct. Approximately 60–70% of ingested fat is absorbed by the intestinal lymphatic system and conveyed to the bloodstream by the thoracic duct [1]. The main component of chyle is fat. The thoracic duct lymph contains from 0.4–5.0 g of fat per 100 ml, and 50–70% of the absorbed fat is conveyed to the bloodstream by way of the thoracic duct [1]. Thoracic duct lymph is not pure chyle, but a mixture of lymphatic fluid originating in the intestine, liver, abdominal wall, and lower extremities. Ninety-five percent of the volume of the thoracic duct lymph originates in the liver and the intestinal tract [1]. This is made up of neutral fat, free fatty acids, sphingomyelin, phospholipids, cholesterol, and cholesterol esters. The total amount of cholesterol ranges from 65 to 220 mg/100 ml. Fatty acids with fewer than 10 carbon atoms in the chain are absorbed directly by the portal venous system [1]. Most of the body's lymphocytes are transported through the thoracic duct system back to the venous system. Lymph circulation performs the vital function of collecting and transporting excess tissue fluid, extravasated plasma protein, absorbed lipids, and other large molecules from the interstitial spaces back to the bloodstream.

Lipid embolism is a dangerous and life-threatening problem and usually arises as a complication of severe trauma associated with long bone or pelvic fractures. It is generally agreed that fat droplets enter the circulation at the site of fracture and cause fat embolism in the brain, kidney, and other areas. Lipids are absorbed from the intestinal tract, transported into pulmonary tissue via the thoracic duct, and exposed to the first catabolic procedures in the lungs [2]. It is not possible for fatty droplets originating from fragments of fractured bone marrow to cause cerebral fat embolism unless alveolar wall destruction takes place due to pulmonary artery occlusion [3]. Neurogenic pulmonary edema creating pathologies can also destroy chylomicron metabolism and lead to cerebral fat embolism [4]. The thoracic duct can convey various cancer seeds [5,6], destructive molecular or chemical agents produced by pancreatic cancers, to the lungs or from the lungs to other organs [7]. Thoracic duct ligation is essential for improving patient survival under such conditions [8]. We expected that cerebral fat embolism may be prevented via thoracic duct ligation in such cases. Our aim was an experimental investigation of whether thoracic duct ligation plays a preventive role against cerebral fat embolism.

Material and Methods

The study was performed using 23 anesthetized hybrid rabbits (3.5±0.4 kg). The experiments were carried out according to the guidelines set out by our faculty's ethics committee on anesthetized and spontaneously breathing rabbits. Three rabbits were used as a control group to provide normal brain and lung samples (Gc, n=3). The remaining animals were divided into two groups: a non-ligated thoracic duct (GI, n=10) and a ligated duct (GII, n=10) group. No food was permitted for six hours before surgery. Balanced injectable anesthesia was used to reduce pain and mortality. After inducing anesthesia with isoflurane using a face mask, 0.2 ml/kg of an anesthetic combination (Ketamine HCL 150 mg/1.5 ml, Xylazine HCL 30 mg/1.5 ml, and distilled water 1 ml) was injected subcutaneously before surgery. During the operation, a 0.1 ml/kg anesthetic combination was used when required. After supradiaphragmatic thoracic duct ligation was applied to GII alone, pulmonary contusion was established in all animals with chest wall and lung injury by dropping a 1-kg cylindrical iron object from a height of 1 meter. Ten days after the procedure, all the rabbits were sacrificed. Rib fractures and petechial or gross hemorrhages on the lung surfaces were regarded as gross lung injury criteria. Lung tissue samples were obtained with parahiliar longitudinal lung samples in 10-{mm sections at the beginning of the multiple branching levels of the pulmonary arteries and were stained with H&E. Alveolar wall destruction, intra-alveolar hemorrhage, and lung edema were regarded as microscopic lung injury criteria. Brain specimens were taken using the frozen-section method at the levels of the middle cerebral artery territories in the parietal lobes and were stained with Sudan Black. Branches occluded through lipid particles of both the middle cerebral arteries were counted on the brain slices in 10 sections and the results were analyzed statistically. Independent sample means were compared with Student's *t* test. A two-tailed *p* value <0.05 was considered statistically significant for all results. Data entry and analysis were performed with SPSS (Chicago, IL) software, version 13.0.

Results

Macroscopically, rib fractures, intraparenchymal hemorrhages, and collections of foamy hemorrhagic fluid in the lungs were observed in all animals. The histopathological appearance of a normal lung is shown in Figure 1. In the traumatized lungs, destruction or loss of ciliary and alveolar cells, intra-alveolar hemorrhage, intra-bronchiolar hemorrhage, alveolar wall rupture, and vascular congestion in the branches of pulmonary arteries were determined in all the animals (Figure 2A,B). These findings in the lungs were more prominent in group GI than in GII. In gross anatomical examinations of the brains, brain swelling, disappearance of the cerebral sulci, cortical and sub-cortical petechial hemorrhagic loci, subarachnoid inflammation, and intravascular fatty-fibrinoid material collections were observed in all animals in GI (Figure 3A,B). In the frozen brain sections the number of branches occluded by fat particles in both the middle cerebral arteries was 4.7±2.45 in two animals of GII compared with 15.5±3.02 in eight animals of GI (Figure 4A,B). There were significantly ($p<0.001$) more occluded branches of the middle cerebral arteries in GI than in GII (Table 1). Thoracic duct ligation prevented the development of both pulmonary artery thrombus and cerebral fat embolism.

Discussion

Lipid embolism is a serious and life-threatening problem. Fat droplets are known to enter the circulation at the site of long bone or pelvic fractures and cause emboli to the brain, kidney, and other areas. Fatty droplets originating from the bone marrow cannot cause cerebral fat embolism unless al-

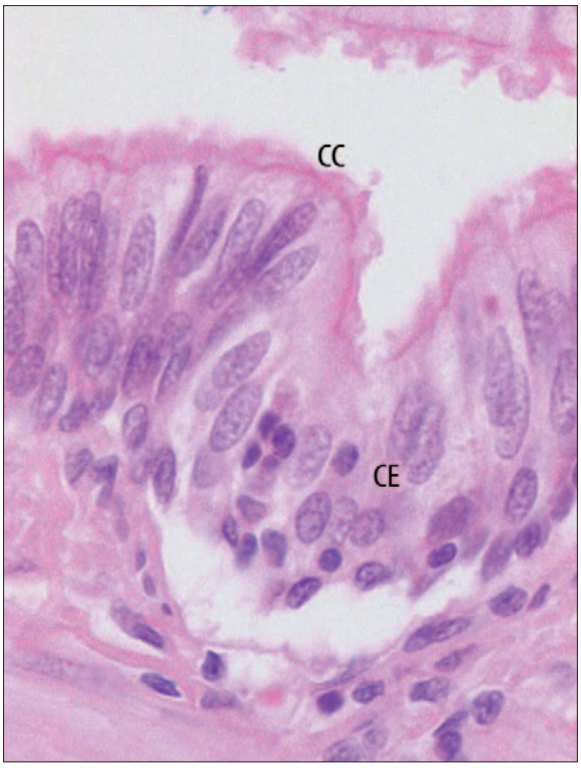

Figure 1. Histopathological appearance of lung tissue of a normal rabbit (CE: columnar epithelial cells of the lungs, CC: ciliary extensions of the columnar cells) LM, H&E, ×100.

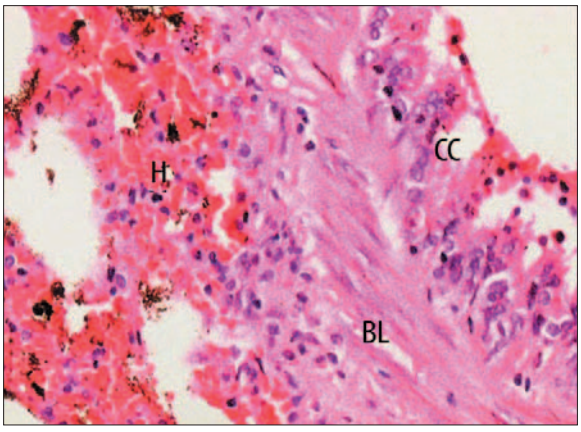

Figure 2A. Histopathological appearance of lung tissue of a traumatized and thoracic duct non-ligated rabbit. Ciliary desquamation, columnar cell atrophy, basal lamina destruction, intra-alveolar hemorrhage, clot formation, and necrotic lung tissue fragments are observed abundantly. (CE: columnar epithelial cells of the lungs, CC: ciliary extensions of the columnar cells, H: hemorrhagic lesions secondary to trauma, BL: basal lamina) LM, H&E, ×100.

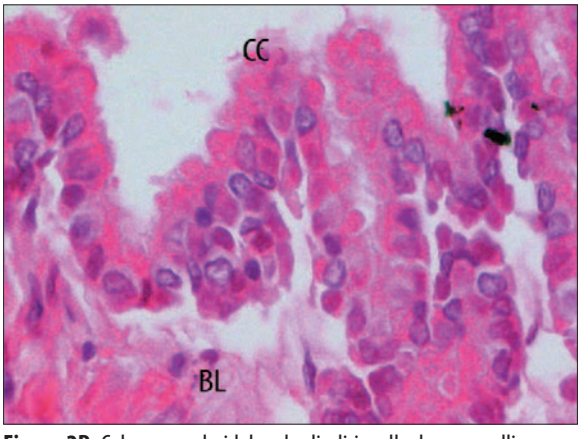

Figure 2B. Columnar cuboidal and cylindiric cell edema, swelling, slightly basal lamina separation, ciliary desquamation, and minimally cellular edema formation are observed in the ligated rabbits' lungs (CC: ciliary extensions of the columnar cells, BL: basal lamina) LM, H&E, ×100.

veolar wall destruction occurs due to pulmonary artery occlusion with bone marrow fragments. Lipids are absorbed from the intestinal tract, transported into pulmonary tissue via the thoracic duct, and exposed to the first catabolic procedures in the lungs. Chylomicron metabolism may be disordered in the destructed lungs and leakage of chylomicrons into the systemic circulation may be facilitated via the destroyed lung barrier after bone fractures. These pathological processes may lead to cerebral fat embolism.

However, cancer metastases and bacterial or parasitic disseminations may be possible through the thoracic duct to the lungs or other organs. In malignancy, malignant and immunological cells have been determined in the thoracic duct [9]. The thoracic duct can lead to various forms of cancer metastasizing to the lungs from other areas or of lung cancers to other organs. Renal cell carcinoma metastases to the lungs can occur through the thoracic duct [5]. Lung cancer is lymphophilic and may spread to neighboring organs via the thoracic duct [6]. Lung cancers can also spread to the other thoracic organs by way of the lymphatics [10]. Various parasites are also spread to the systemic circulation through the thoracic duct. *Strongyloides* larvae and other pathogens can transverse the lymphatics to the thoracic duct and can then pursue a lymphohematogenous dissemination to the lungs [11]. In addition, destructive molecular or chemical agents can be transferred by the thoracic duct and result in lung injury. For example, in severe acute pancreatitis (SAP), the mechanisms leading to adult respiratory distress syndrome (ARDS) are usually attributed to the release of active enzymes and vasoactive substances from the pancreas to the lungs. Thoracic duct drainage has been proposed as a means of removing that part of these substances that drains through retroperitoneal lymphatics before they reach the systemic circulation. These results suggest that in patients with ARDS due to SAH, cytokines as well as pancreatic enzymes may contribute to the development of lung injury, and that lymphatics are potential vectors of these mediators [7,12]. Pancreatic enzymes can be transported in the lungs via the thoracic duct and result in pleuropulmonary complications. Thoracic duct ligation can protect the lungs in such situations [13]. T lymphocytes and eosinophils are important components of the inflammatory cell infiltrate in bronchial mucosa in asthma. Granulocyte/macrophage colony-stimulating factors of the intestinal mucosa reaching the thoracic duct may play an important role in the pathogenesis of bronchial asthma [14]. Thoracic duct drainage may be effective in removing toxic substances released from the inflamed pancreas and responsible for lung damage.

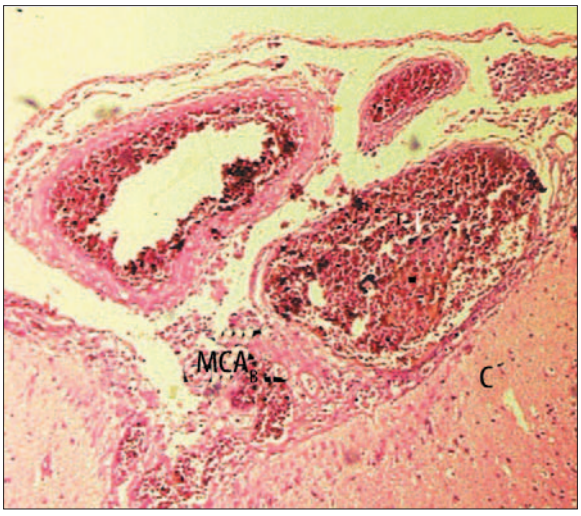

Figure 3A. Subarachnoidal inflammation, leptomeningeal thickness, vascular endothelial injury, intraluminal stasis, fatty-fibrinoid material collections, and clotting in the middle cerebral artery branches are observed abundantly in all animals of GI (MCAB: middle cerebral artery branches, C: cortex cerebri; T: stasis and thrombus nidus) LM, H&E, ×100.

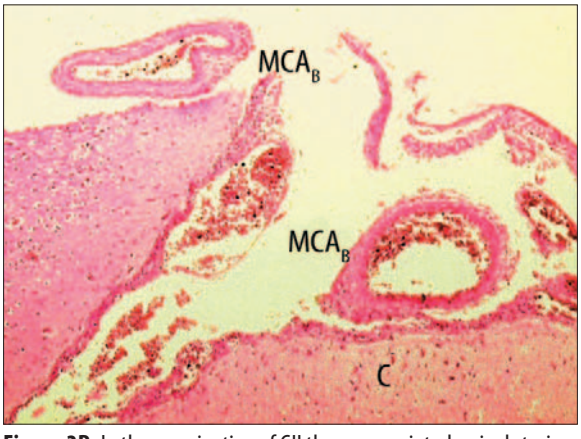

Figure 3B. In the examination of GII there are no intraluminal stasis, fatty-fibrinoid material collections, or clotting observed in the middle cerebral artery branches (MCAB: middle cerebral artery branches, C: cortex cerebri) LM, H&E, ×100.

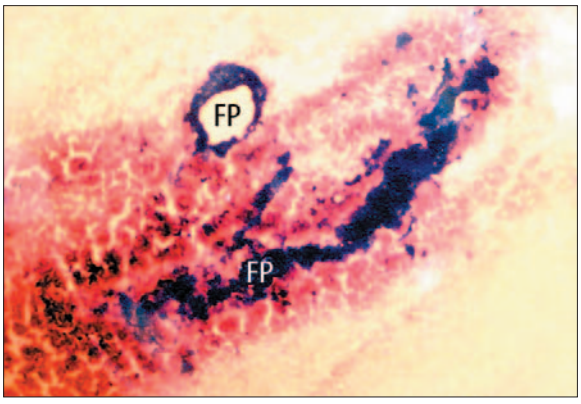

Figure 4A. A large number of middle cerebral artery branches occluded with fat particles are seen (FP) in GI. LM, Sudan III, ×100.

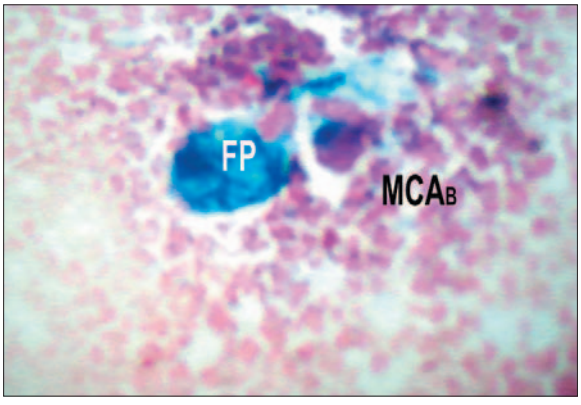

Figure 4B. A lower number of middle cerebral artery branches occluded with fat particles are seen (FP) in GII. LM, Sudan III, ×100.

Table 1. Numbers of occluded branches of middle cerebral arteries.

Animals	Numbers of all occluded middle cerebral artery branches on both sides
Normal group (Gc, n=3)	–
No thoracic duct ligation group (GI, n=10)	15.5±3.02 (n=8)
Thoracic duct ligation group (GII, n=10)	4.7±2.45 (n=2)

Adult respiratory distress syndrome due to alveolar capillary membrane injury is related to necrotizing pancreatic enzymes arriving from the pancreas via the thoracic duct. Thoracic duct external drainage is essential in order to improve survival levels in such patients [8].

Drainage of the thoracic duct in the treatment of severe forms of bronchial asthma may be an effective mode of treatment [15]. Plastic bronchitis may be seen after palliative surgery for cyanotic heart disease and palliative surgery for cyanotic heart disease in which ligation of the thoracic duct results in partial resolution [16]. One case of *Pneumocystis carinii* pneumonia was induced through immunosuppression following thoracic duct ligation [17].

Chylothorax is a life-threatening clinical entity, the majority of cases of which resolve with non-operative management. Spontaneous chylothorax is uncommon and may originate from pulmonary lesions. It was successfully treated with a medium-chain triglyceride diet in one study [18]. Chylous fistulas have been reported to be completely cured by the application of an intraductal chemical agent (OK-432) [19]. Spontaneous chylothorax may also occur in lung injuries. The traditional surgical management of cases refractory to conservative treatment is thoracic duct ligation [20]. Surgical techniques reported in the literature include parietal pleurectomy, pleurodesis, ligation of leaking lymphatics, pleuroperitoneal shunts, thoracic duct ve-

nous anastomosis, and ligation of the thoracic duct [21]. Transabdominal ligation of the thoracic duct is the treatment of choice for postoperative chylothorax after esophagectomy [21,22]. Thoracoscopic ligation of the thoracic duct provides safe and effective treatment and may obviate the use of thoracotomy and the problems associated with a major thoracic procedure. Because of our previous clinical experience, we favor low ligation of the thoracic duct, with mass ligation of all tissue between the aorta and azygos vein just above the diaphragmatic hiatus.

This study aimed to investigate whether or not thoracic duct ligation prevents cerebral fat embolism in lung injury. Pulmonary contusion was established in all 20 rabbits (n=20) and thoracic duct ligation was applied to half (n=10). Twenty days after the procedure, all the rabbits were sacrificed. Their brains and lungs were observed histopathologically. Lung injury was more prominent in the non-ligated thoracic duct (GI) than in the ligated thoracic duct group (GII). The branches occluded through lipid particles in both the middle cerebral arteries were more numerous in GI than in GII ($p<0.001$). In conclusion, thoracic duct ligation had more beneficial effects in terms of prevention of cerebral fat embolism.

Conclusions

We noted that cerebral fat embolism is a dangerous complication of lung injury. Thoracic duct ligation is essential for the improvement of survival rates in such conditions [23]. Laparoscopic or thoracoscopic ligation of the thoracic duct can be performed. These procedures have been reported to be successful, with resolution of chylothorax being achieved [24]. In summary, we believe that thoracic duct ligation has a preventive effect on the development of cerebral fat embolism in patients with lung injury.

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