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ROLE OF THE DUCTUS THORACICUS IN PULMONARY FAT EMBOLISM AFTER SUBARACHNOID HAEMORRHAGE: A PRELIMINARY EXPERIMENTAL STUDY

SUBARAKNOİD KANAMA SONRASI GELİŞEN PULMONER YAĞ EMBOLİSİNDE DUCTUS THORACICUS'UN ROLÜ: ÖN DENEYSEL ÇALIŞMA

Hakan KINA[1], Muhammet ELVEREN[2]

[1]Department of Neurosurgery, İstinye University Gaziosmanpaşa Medical Park Hospital, İstanbul, Türkiye
[2]Department of Neurosurgery, Atatürk University, Erzurum, Türkiye

ORCID IDs of the authors: H.K. 0000-0002-9741-7720; M.E. 0000-0002-9720-5605

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ABSTRACT

Objective: Subarachnoid haemorrhage is a multisystemic disease due to its effects on the autonomic nervous system. Pulmonary tissues may be affected due to its effects on the intestinal system, lipid metabolism, and ductus thoracicus in subarachnoid haemorrhage. This study demonstrate the pathophysiology of pulmonary fat embolism after sympathetic activation of the ductus thoracicus with lipid absorption disorders after subarachnoid haemorrhage.

Material and Methods: In the study, 24 male rabbits were used, of which five were selected as the control group (GI) and five as the SHAM group (GII). The SHAM group was injected with a 0.7 mL isotonic solution into the cisterna magna. The study group (GIII) was injected with 0.7 mL autologous blood into the cisterna magna. The lymphatic vessels in the middle sections of the duodenum, the thoracic duct portions opening into the jugular vein, and the terminal branches of the pulmonary arteries were examined and counted.

Results: The thoracic duct vasospasm index (VSI) values and numbers of branches occluded by fat particles in the pulmonary arteries were: 1.65±0.22/3.21±0.54 in GI, 1.97±0.34/7.3±2.4 in GII, and 2.54±0.56/14.53±14.53 in GIII. In the six subjects with severe thoracic duct spasm in GIII, the number of pulmonary arteries occluded with chylomicrons was higher (p>0.00001). P values among groups were: p > 0.05 in GI/GII; p<0.005 in GII/GIII and p<0.0001 in GI/GIII.

Conclusion: This is the first experimental study conducted on animals investigating the lipid metabolism disorder associated with subarachnoid haemorrhage affecting the cervical ganglia, thoracic duct spasm, and pulmonary fat embolism.

Keywords: Subarachnoid haemorrhage, thoracic duct, chylomicrons, pulmonary fat embolism

ÖZET

Amaç: Subaraknoid kanama, otonom sinir sistemi üzerindeki etkileri nedeniyle multisistemik bir hastalıktır. Subaraknoid kanamada intestinal sistem, lipid metabolizması ve duktus torasikus üzerindeki etkileri nedeniyle pulmoner dokular etkilenebilir. Bu çalışma, subaraknoid kanamadan sonra lipid emilim bozuklukları ile birlikte duktus torasikusun sempatik aktivasyonundan sonra pulmoner yağ embolisinin patofizyolojisini göstermeyi amaçlamıştır.

Gereç ve Yöntem: Çalışmada kullanılan 24 erkek tavşandan beşi kontrol grubu (GI), beşi SHAM (GII) olarak seçildi ve SHAM grubunda sisterna magnaya 0,7 mL izotonik enjekte edildi. Çalışma grubunda (GIII) ise sisterna magnaya 0,7 mL otolog kan enjekte edildi. Deneklerin duodenum orta kısımlarındaki lenf damarları, juguler vene açılan torasik duktus kısımları ve pulmoner arterlerin terminal dalları incelendi ve sayıldı.

Bulgular: Duktus torasikus vazospazm indeks (VSI) değerleri ve pulmoner arterlerde yağ parçacıkları tarafından tıkanan dal sayıları: GI'de 1,65±0,22/3,21±0,54, GII'de 1,97±0,34/7,3±2,4 ve GIII'te 2,54±0,56/14,53±14,53 idi. GIII'te şiddetli duktus torasikus spazmı olan altı denekte, şilomikronlarla tıkanmış pulmoner arter sayısı daha yüksekti (p>0,00001). Gruplar arasındaki p değerleri: GI/GII'de p>0,05; GII/GIII'te p<0,005 ve GI/GIII'te p<0,0001 idi.

Sonuç: Çalışmamız; subaraknoid kanama sonrası gelişen lipid metabolizması bozukluğunun, servikal ganglionlar, duktus torasikus spazmı ve pulmoner yağ embolisi ile ilişkisini araştıran ilk deneysel çalışmadır.

Anahtar kelimeler: Subaraknoid kanama, torasik duktus, şilomikronlar, pulmoner yağ embolisi

Corresponding author/İletişim kurulacak yazar: Hakan KINA – kinahakan@gmail.com

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INTRODUCTION

Subarachnoid haemorrhage is an important disease with intracranial and extracranial complications causing increased mortality and morbidity. Subarachnoid haemorrhage triggers an inflammatory process and causes multisystemic pathologies (1, 2). Subarachnoid haemorrhages affect the autonomic nervous system through the activation of the sympathetic system and cause extracranial complications (2). The most common site of extracranial complications is the pulmonary system, often presenting with neurogenic pulmonary oedema (3). Pulmonary oedema may present with non-specific findings such as dyspnoea, tachypnoea, tachycardia, and fever, which are commonly observed in the clinical findings of pulmonary fat embolism (4, 5). Fat embolism is a non-traumatic systemic disease with multiple causes, often occurring after orthopaedic trauma. Fat embolism results from the pathological processes of lipid production and transport in the intestinal tract. In the pathophysiology of pulmonary fat embolism, chylomicrons and the ductus thoracicus, which allows chylomicrons to enter the systemic circulation, are involved (5, 6). The ductus thoracicus is structurally 38-45 cm long and 2-5 mm in diameter, located between L2 and the lower cervical region. The sympathetic nervous system predominantly innervates this region. In a pathology such as subarachnoid haemorrhage, where the sympathetic response is dominant, an increase in the contraction of the ductus thoracicus is expected (7, 8). Pulmonary fat embolism may occur with the involvement of the ductus thoracicus accompanied by lipid metabolism disorders (5). In our study, we histopathologically examined the effect of subarachnoid haemorrhage on the cervical ganglia, lipid absorption changes in the intestines, and its impact on the ductus thoracicus and pulmonary tissues.

MATERIAL AND METHODS

A total of 24 rabbits, aged 2.5±0.1 years and weighing 4±0.5 kg, were used in the study. The principles of the "Guidelines for the Care and Use of Laboratory Animals" were applied. This study received ethics committee approval from the Atatürk University Local Ethics Council of Animal Experiments (Date: 18.08.2022, No: 166). Five subjects were randomly selected as the control group (GI), five as the SHAM group (GII), and 14 as the study group (GIII).

The SHAM group and the subjects included in the study group were first anaesthetised with 0.2 mL/kg isoflurane and subcutaneously with 50 mg/1.5 mL Ketamine HCL. General anaesthesia was maintained with the injection of 30 mg/1.5 mL Xylazine HCL and 1 mL distilled water. After the occipital-cervical region was prepared for the surgical conditions, the subject's head was hyperflexed, and the cisterna magna was accessed after the posterior notch of the foramen magnum was identified. Once it was confirmed that there was no bleeding by aspirating 1 mL of cerebrospinal fluid, 0.5 mL of isotonic solution was administered to the SHAM group, and 0.5 mL of autologous blood taken from the ear arteries was administered to the cisterna magna in the study group. Vital signs were monitored twice daily during the experiment. After three weeks of follow-up, the animals were euthanized under general anaesthesia with an intracardiac injection of 2 mL of 10% formalin solution. They were then decapitated at the level of the 7th cervical vertebra to examine the third vagal nerve networks and cervical sympathetic ganglia. The cervical, duodenal, and lung tissues were incubated in formalin solution for three days. To analyse the thoracic ducts, the supraclavicular regions were excised along with the surrounding tissues, including the subclavian vessels, axillary nerves, and thoracic ducts. The paravertebral deep soft tissues on both the right and left sides were removed together. The sympathetic ganglia and thoracic ducts were fixed in formalin and dissected with the help of an operating microscope for histological examination. Twenty consecutive 5-m sections were prepared from the tissue samples. They were stained with haematoxylin-eosin, oil red, and aldehyde fuchsin and examined under a light microscope. Data were analysed using a commercially available statistical software package SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Data analysis consisted of the Kruskal-Wallis and Mann–Whitney U tests. Differences were considered significant at $p<0.05$.

RESULTS

Histopathological analysis revealed stellate ganglion degeneration in the subjects of the subarachnoid haemorrhage model group (Figure 1). In this group, fat and protein droplets of lymphatic content were observed on the duodenal wall, particularly under the serosa, in subjects with spasms in the thoracic duct (Figure 2). Dilatation of lymphatic vessels, hydropic degeneration of endothelial cells, and enlargement of Peyer's patches were observed. Fluid accumulation was also detected around the blood vessels and within the lymphatic vessels. Swelling of the lymph nodes in these areas and dilatation of the distal lymphatic ducts were noted (Figure 3). In subjects who developed spasms in the region where the ductus thoracicus opens into the subclavian vein, luminal narrowing of the thoracic ducts, contraction of myocyte, and degeneration of endothelial cells were observed. High fatty components were detected in the thoracic ducts with spasms (Figures 4, 5). Finally, pulmonary tissue examination revealed lipid droplets in the lung tissues of the haemorrhage group (Figure 6). The thoracic duct vasospasm index (VSI) values and fat particle density counts in the pulmonary arteries were as follows: 1.65±0.22/3.21±0.54 in GI, 1.97±0.34/7.3±2.4 in GII, and 2.54±0.56/14.53±14.53 in GIII. Severe thoracic duct spasm was more common in GIII, affecting six subjects where fat cells were densely present in the pulmonary arteries. The P-values between the groups were as follows: $p>0.05$ between GI and GII, $p<0.005$ between GII and GIII, and $p<0.0001$ between GI and GIII (Table 1).

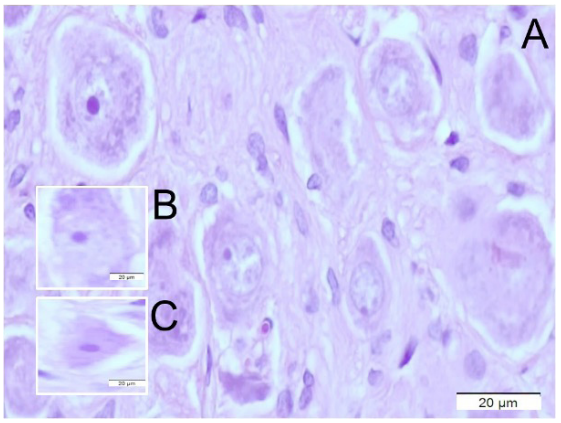

Figure 1: Normal stellate ganglion neurones belong to GI (A), moderately degenerated neurones in GII (B), and severely degenerated neurones are seen (C). Degenerated neurones have neurodegeneration criteria such as cellular angulation, shrinkage, nuclear halo formation and condensation (LM, H&E, x40)

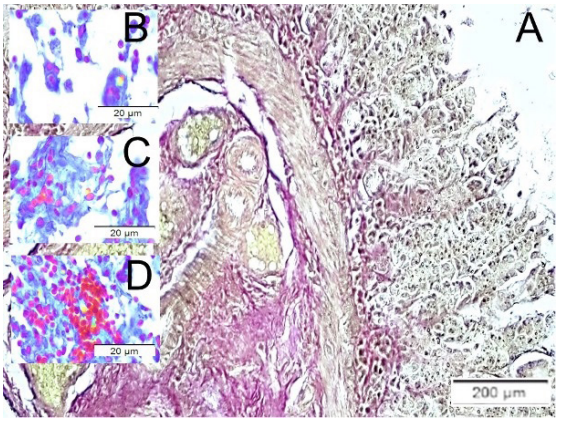

Figure 2: Duodenal histomorphology (A) and chylomicron droplets (Yellow/red) in GI (B); GII (C) and GIII (D) animals (LM, Oil Red, x4/A, x40/B-D)

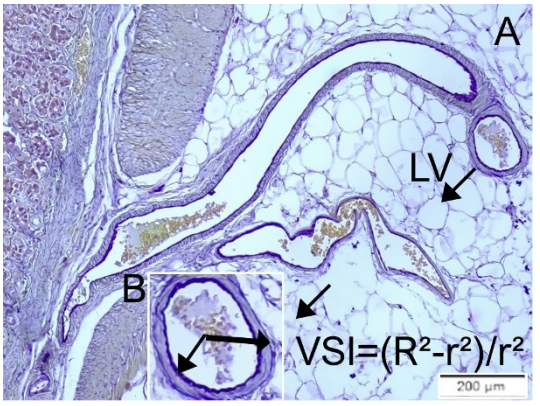

Figure 3: The calculation method of duodenal lymph vessels (LV) and vasospasm index (VSI) in a normal subject is followed (LM, Aldehyde Fuchscine, x4)

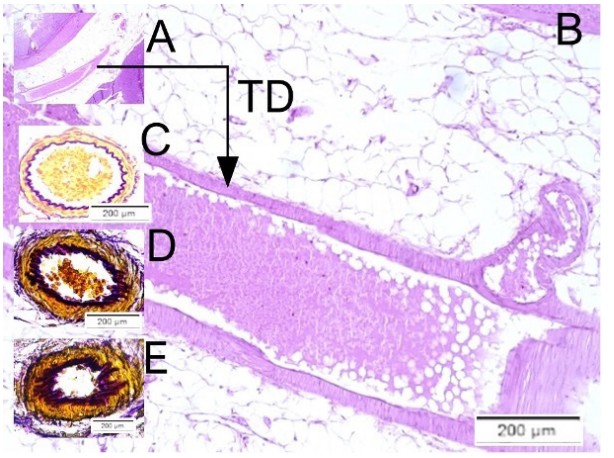

Figure 4: The longitudinal (A-B) and vertical section (C) of the thoracic duct of a normal subject, the vertical section of the thoracic duct of a subject belonging to the SHAM group (D), and the vertical section of the thoracic duct of a subject belonging to the study group are observed. Degenerated endothelial cells have neurodegeneration criteria such as cellular angulation, shrinkage, nuclear halo formation and condensation (LM, H&E/A; Aldehyde Fuchscine/C-E, x4)

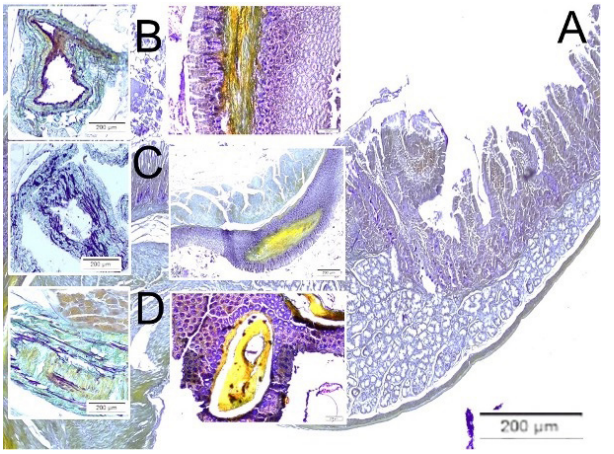

Figure 5: The histopathological structures of the thoracic duct sections (left column) and duodenal lymph channels (right column) in the GI (A-B), GII and GIII groups are observed. While minimal toric canal spasm and an LNF fluid lake in the duodenum wall are observed in GII (C); There is marked spasm in GIII and a significant lymphoid fluid collection in the duodenal wall (LM, Aldehyde fuchscine, x4)

DISCUSSION

Lymph fluid drains into the venous system through the lymphatic ducts, specifically the thoracic and right lymphatic ducts. The thoracic duct is the largest and is responsible for the lymphatic drainage of the entire body, except the head, neck, and right side of the chest. Its function is to return the lymph to the circulatory system. Structurally, the thoracic duct is 38–45 centimetres long and 2–5 millime-

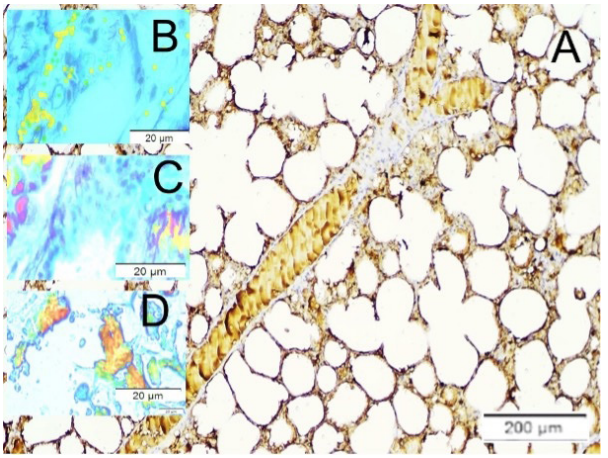

Figure 6: Pulmonary tissue (A) and chylomicron droplets (Yellow/Red) in GI (A-B); GII (C)and GIII (D) animals (LM, H&E/A; Oil Red/B-D, x40)

stimulation predominates (7, 8). In Telinius et al., electrical field stimulation increased contractions in the ductus thoracicus. Using a muscarinic receptor blocker (atropine) and an α-adrenoceptor blocker (phentolamine), they showed that sympathetic innervation has a significant effect on the ductus thoracicus, almost completely eliminating contractions caused by stimulation (8). The lungs are exposed to particles or toxic agents in the environment, and a robust lymphatic system is essential for protecting them. The lymphatic system is complex, consisting of collateral branches, lymphatic capillaries, local lymph nodes, lymph trunks, and larger ducts like the ductus thoracicus, all working together. Inflammatory processes can disrupt the lymphatic flow, causing impairment (11, 12). Chylomicrons are lipoprotein particles formed during the absorption of fats from the intestines. Fatty acids and monoglycerides absorbed from the intestine are converted into chylomicrons by enterocytes, which then enter the lymphatic system (13, 14).

Table 1: Comparison of thoracic duct vascular severity index (VSI), pulmonary artery fat particle density, and severe thoracic duct spasm results among the control (GI), SHAM (GII), and study (GIII) groups

	Thoracic duct VSI	Pulmonary artery fat particle density	Severe thoracic duct spasm (Number/Total)	P values compared to GI	P values compared to GII
GI (Control group)	1.65±0.22	3.21±0.54	0/5	-	-
GII (SHAM group)	1.97±0.34	7.3±2.4	0/5	p>0.05	-
GIII (Study group)	2.54±0.56	14.53±14.53	6/11	p<0.0001	p<0.005

VSI: Thoracic duct vasospasm index

tres in diameter, located between L2 and the lower cervical region. A typical anatomical description of the thoracic duct is found in approximately 50% of individuals, with the remainder displaying variations in anatomy. The thoracic duct most commonly (95%) terminates in the internal jugular vein, the subclavian vein, or at the junction between the two. It is often composed of a single vessel, although variations involving two or more vessels may occur (9). Lymph from the thoracic duct returns to the bloodstream through the lymphovenous junction. The lymphovenous valve regulates and protects the lymph flow, often being bicuspid to prevent the lymph from escaping back and the blood from entering the lymphatic system. However, a cadaveric study by O'Hagan et al. found this valve to be absent in approximately 30% of individuals, raising questions about its function (10). The ductus thoracicus is activated by both adrenergic (predominantly) and cholinergic components. It is known to carry lymph to the venous system through spontaneous contractions of the lymphatic vessel wall, independent of systemic effects, but the mechanisms of this coordination and modulation are not yet understood. In pathologies where the sympathetic system is triggered, increased venous flow in the lymph vessels is expected in the ductus thoracicus, where adrenergic

Chylomicrons travel from the small intestine through the ductus thoracicus into the lymphatic system, eventually entering the bloodstream. This process is critical for the efficient transport and distribution of fats and lipids throughout the body (15, 16). Fat embolism occurs when fat droplets or particles enter the bloodstream. This condition is often associated with trauma, surgical operations, adipose tissue damage, or inflammatory processes and can be fatal. Excessive fat in chylomicrons can lead to a pathological process, increasing free fatty acids and fat droplets, which may trigger the formation of fat emboli. These emboli, which are the remnants of chylomicrons or other lipid particles, can enter the bloodstream. Although chylomicrons play an essential role in fat transport, pathological conditions can link their metabolism to fat embolism. Although the mechanisms remain under investigation, they require further study (6, 17). Regardless of the pathophysiological mechanism, fat entering the circulation can result in fat embolism, causing clinical signs in various systems, including neurological, cardiac, and pulmonary. Fat embolism has many causes, including orthopaedic trauma (most common), liver injury, cardiopulmonary resuscitation, transplantation, liposuction, poisoning, and caesarean section

(6, 18, 19). Symptoms include respiratory (the most common), cardiac, neurological, and dermatological issues. The lack of specific laboratory tests and clinical findings makes diagnosing fat embolism challenging. Radiologically, it presents with capillary occlusion in the pulmonary and brain systems, leading to non-specific findings like petechial haemorrhages, oedema, and ground-glass opacities, which are common in other conditions affecting these systems. Fat embolism triggers an inflammatory process, but each underlying cause induces a unique inflammatory response. While the exact mechanism is unclear, it is likely that a fat embolism develops because of this inflammation (5, 6). Despite the complexity of fat embolism's pathophysiology and the lack of definitive diagnostic methods, some criteria have been proposed. Among these, the Gurd and Wilson criteria are the most widely used. The major criteria included respiratory distress, cerebral symptoms in non-head injury patients, petechial rash, renal and retinal changes, haemoglobin drop, new-onset thrombocytopenia, elevated erythrocyte sedimentation rate, and fat macroglobulinemia. Minor criteria included tachycardia (>110 bpm), fever (>38.5°C), and jaundice. The diagnosis can be made with two major criteria or one major and three minor criteria (6, 20). Pulmonary capillaries and small blood vessels are often the first to be affected, resulting in hypoxia, increased capillary permeability, and pulmonary oedema. However, the exact mechanism of this oedema remains unclear (5, 21). Subarachnoid haemorrhage is a well-known condition with significant morbidity and mortality. The most common extracranial complication is pulmonary oedema caused by sympathetic hyperactivity, but its pathophysiology and clinical presentation are not well understood (22). Neurogenic pulmonary oedema shares non-specific findings with pulmonary fat embolism, such as dyspnoea, tachypnoea, hypoxia, tachycardia, and fever (3). The prevalence of pulmonary embolism secondary to subarachnoid haemorrhage is unknown. However, according to Davidson et al., the clinical prevalence is 31%, while the autopsy prevalence is 78% (3). The most emphasised pathophysiological mechanism is the pulmonary venule response to adrenergic hypersensitivity (22). Sympathetic hyperactivity affects the cervical ganglia, increasing catecholamine levels, diverting blood from the systemic to the pulmonary circulation, and increasing pulmonary blood volume and capillary permeability. This dual impact on the central and pulmonary systems releases inflammatory mediators, triggering systemic immune responses (22-24). Studies have highlighted cervical ganglia's role in systemic inflammation following subarachnoid haemorrhage (25, 26). Zhang et al. showed that stellate ganglion blockade in subarachnoid haemorrhage patients reduced middle cerebral artery vasospasm and inflammatory mediator release (26). Limited studies exist on lipid profile changes in subarachnoid haemorrhage patients. Dhandapani et al. reported lipid peroxidation disorders and elevated triglyceride levels (27). Pilitsis et al. showed increased free fatty acid levels and vasospasm following subarachnoid haemorrhage (28).

This study has several limitations. First, although the sample size of 24 rabbits is sufficient for an experimental model, it is relatively small and may limit the generalizability of the findings. Second, while the rabbit model provides valuable insights, it may not fully replicate human physiological responses to subarachnoid haemorrhage and pulmonary fat embolism, limiting the direct applicability of the results to clinical settings. Third, the follow-up period was restricted to three weeks, and the longer-term effects of subarachnoid haemorrhage on lipid metabolism and pulmonary fat embolism were not assessed, leaving potential chronic changes unexplored. In addition, although the study demonstrated the pathophysiological role of the ductus thoracicus and sympathetic activation, no direct intervention, such as sympathetic blockade, was performed. Such interventions could have provided further clarity on the mechanisms behind the observed changes. Finally, the study primarily focused on histological findings, without incorporating functional assessments such as pulmonary function tests or direct measurements of lipid metabolism, which limits the clinical relevance of the histopathological outcomes.

CONCLUSION

Subarachnoid haemorrhage is an intracranial pathology, but it is also a systemic disease because it affects the autonomic nervous system and triggers inflammation. In our animal study, we demonstrated that the effects of the sympathetic system on the lipid profile and the ductus thoracicus after subarachnoid haemorrhage can influence pulmonary tissues, as observed in histological sections. This study on the pathophysiological mechanism should be further validated with studies involving cervical sympathetic ganglion blockade, whether through electrical, pharmacological, or surgical methods.

Availability of Data and Materials: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethics committee approval was received for this study from the the Atatürk University Local Ethics Council of Animal Experiments (Date18.08.2022, No: 166).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- H.K., M.E.; Data Acquisition- H.K.; Data Analysis/Interpretation – H.K., M.E.; Drafting Manuscript- H.K.; Critical Revision of Manuscript- M.E.; Final Approval and Accountability- H.K., M.E.

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