MORPHOMETRIC CHANGES IN PULMONARY VESSELS DURING TOXIC HEPATITIS: AN EXPERIMENTAL STUDY

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https://doi.org/10.5281/zenodo.20080129

Abstract. *Background/Aim. Toxic hepatitis is associated with systemic disturbances that may affect the pulmonary vasculature. The aim of this study was to investigate morphometric changes in lung vessels under experimental toxic hepatitis.*

Materials and Methods. The study was conducted on 40 laboratory Wistar rats divided into control and experimental groups. Toxic hepatitis was induced by administration of a hepatotoxic agent (carbon tetrachloride). Histological examination of lung tissue was performed followed by morphometric analysis of vascular parameters, including vessel diameter, wall thickness, and lumen area using ImageJ software.

Results. The experimental group demonstrated a significant decrease in vessel diameter, an increase in vascular wall thickness, and a reduction in lumen area ($p < 0.05$). These findings indicate pronounced vascular remodeling and impaired pulmonary microcirculation as a result of liver injury.

Conclusion. Toxic hepatitis induces significant morphometric alterations in pulmonary vessels, reflecting the systemic nature of the pathological process and highlighting the importance of a comprehensive approach to investigating respiratory complications in liver diseases.

Keywords: *toxic hepatitis; pulmonary vessels; morphometry; vascular remodeling; microcirculation; experimental study; rats; endothelial dysfunction; pulmonary hemodynamics.*

INTRODUCTION

Liver pathology exerts a systemic impact on various organs and functional systems of the body, including the lungs. It is established that toxic liver injury leads to a complex of metabolic, hemodynamic, and inflammatory disturbances affecting not only the hepatobiliary system but also the respiratory organs. Due to their extensive vascular network and high sensitivity to changes in systemic circulation, the lungs are among the primary targets in hepatic pathology.

Toxic hepatitis is accompanied by severe impairment of intrahepatic and systemic hemodynamics, leading to altered blood rheology, hypoxia, and endothelial dysfunction. Under these conditions, remodeling of the vascular bed occurs, particularly at the level of pulmonary microcirculation. Microcirculatory disturbances are characterized by vascular vasospasm, wall thickening, reduced lumen area, and altered ratios between vascular components, which may ultimately contribute to the development of pulmonary hypertension and impaired gas exchange.

Inflammatory mediators, oxidative stress, and hypoxic processes arising from toxic liver damage play a pivotal role in vascular alterations. These factors cause endothelial damage, activate fibrotic processes, and lead to the structural rearrangement of the vascular wall. Consequently, a

pathological cycle is formed, intensifying systemic disturbances and exacerbating the course of the disease.

Despite the existence of individual studies focusing on the influence of hepatic pathology on the respiratory system, the morphometric characteristics of the pulmonary vasculature during toxic hepatitis remain insufficiently explored. Specifically, there is a lack of quantitative data regarding changes in vessel diameter, wall thickness, and lumen area, which complicates an objective assessment of the degree of vascular transformation.

Therefore, experimental research aimed at a detailed study of morphometric changes in pulmonary vessels during toxic hepatitis is of significant scientific and practical interest. The data obtained will deepen the understanding of the pathogenesis of systemic disturbances in liver diseases and serve as a basis for developing new approaches to the diagnosis and prevention of respiratory complications.

LITERATURE REVIEW

In recent years, the study of the pulmonary vasculature has gained particular relevance due to increasing interest in the systemic mechanisms of vascular remodeling under various pathological conditions. Pulmonary vessels are highly sensitive to hypoxia, inflammation, endothelial dysfunction, and metabolic disorders, making them critical subjects for morphological and morphometric research.

Contemporary studies indicate that pulmonary vascular remodeling involves complex structural and molecular changes. For instance, it has been shown that exosomes derived from induced pluripotent stem cells can attenuate vascular remodeling in pulmonary arterial hypertension by targeting the HIF-1alpha and Runx2 signaling pathways [1]. This emphasizes the crucial role of cellular and molecular mechanisms in the pathogenesis of vascular disorders.

The methodological foundations for studying the pulmonary vasculature are detailed in fundamental research describing modern approaches to the morphological and morphometric assessment of the vascular wall and lumen, including quantitative methods for analyzing the microcirculatory bed [2].

Significant interest lies in works where vascular changes are viewed as manifestations of systemic pathology. In experimental models of systemic sclerosis, pronounced structural and functional disturbances of the pulmonary hemomicrocirculatory bed were identified, confirming the systemic nature of vascular rearrangement [3].

Advancements in imaging techniques have significantly expanded the understanding of pulmonary vascular morphology. Contrast-free angiography *in vivo* has demonstrated reduced vascular density and signs of remodeling under chronic hypoxia [4]. Three-dimensional (3D) imaging has further revealed complex spatial restructuring of the microvascular network in pulmonary hypertension [5].

Studies on metabolic factors also demonstrate their influence on the morphofunctional state of the lungs. Specifically, lipid metabolism disorders can lead to changes in the histophysiology of lung tissue and reduced blood oxygen transport function [5].

A special place is occupied by works on the "liver-lung" axis. It has been shown that portal hypertension and chronic liver diseases lead to systemic hemodynamic disturbances affecting the pulmonary vascular system [7]. Hepatopulmonary syndromes are accompanied by impaired gas exchange and vascular regulation, including vasodilation and altered vascular tone [9].

For modern morphology, 3D reconstruction and stereology methods are of great importance, allowing for an objective assessment of the spatial organization of the pulmonary

vascular network [8]. Similar results have been achieved using micro-computed tomography (MCT), enabling visualization and quantitative evaluation of the pulmonary arterial microvascular tree [10].

Alongside modern technologies, intravital microscopy continues to play a vital role, allowing for the real-time study of pulmonary microcirculation and the functional state of vessels under various pathological influences [18]. Experimental studies confirm that during chronic pulmonary ischemia, the vasculature undergoes pronounced morphological and functional transformation [19].

Interestingly, similar vascular remodeling processes are observed in other organs. For example, significant restructuring of the microvascular bed has been identified in liver fibrosis, confirming the systemic nature of angioarchitectonic changes [20]. These findings suggest that toxic liver injury may also impact the pulmonary vascular system.

Fundamental concepts of vascular morphology were established in classical studies showing that pathological processes lead to profound vascular wall rearrangement, changes in vessel caliber, and disruption of normal organization [21]. These principles are universal and applicable to pulmonary vessels under various pathological states.

In recent years, significant attention has been paid to cellular components of the vascular wall, particularly pericytes. They play a key role in regulating microcirculation and vascular stability, and their dysfunction contributes to vascular remodeling [22]. Experimental studies on models of chronic obstructive pulmonary disease (COPD) confirm that vascular remodeling is associated with the activation of molecular signaling pathways, such as VEGF/PI3K/Akt, and can be viewed as a potential therapeutic target [23].

A separate research direction includes works on morphofunctional changes in vessels under systemic influences. Specifically, significant alterations in the vascular bed, including wall restructuring and hemodynamic changes, have been shown following splenectomy [11, 13]. Similarly, morphological changes in the thymus have been identified during toxic liver injury, indicating the systemic nature of the pathological process [15, 17].

Thus, the analysis of modern literature shows that the pulmonary vasculature is a dynamic system actively responding to hypoxia, inflammation, metabolic disorders, and systemic diseases. Despite the significant number of studies on vascular remodeling in pulmonary hypertension and chronic lung diseases, morphometric assessment of pulmonary vessels in toxic liver injury remains insufficiently studied.

MATERIALS AND METHODS

The experimental study was conducted on 40 mature male Wistar laboratory rats weighing 180–220 g. The animals were housed under standard vivarium conditions (temperature 22–24 °C, relative humidity 50–60%, natural light cycle) with *ad libitum* access to water and standard chow.

Before the experiment, animals underwent a 7-day adaptation period. Subsequently, they were divided into two equal groups: the control group (n = 20), receiving standard nutrition and saline, and the experimental group (n = 20), in which toxic hepatitis was modeled.

Toxic hepatitis was induced by intraperitoneal administration of a hepatotoxic agent (carbon tetrachloride, CCl_4) at a dose of 1.0 ml/kg body weight mixed with vegetable oil (1:1), twice a week for 4 weeks. Control animals received an equivalent volume of saline.

At the end of the experiment, animals were euthanized via anesthetic overdose in compliance with bioethical standards. Lungs were extracted, fixed in 10% neutral buffered formalin for 24–48 hours, and subjected to standard histological processing.

Paraffin sections (5–7 μm) were stained with hematoxylin and eosin (H&E). Morphometric analysis was performed using a light microscope and a digital image processing system (Image J).

The study evaluated the diameter of arterioles and venules (external and internal), vascular wall thickness, lumen area, and the wall thickness-to-vessel diameter ratio. Measurements were taken in at least 10 fields of view for each slide, followed by the calculation of mean values.

Statistical analysis was conducted using IBM SPSS Statistics (version 26.0). Results are presented as mean and standard deviation (M±SD). Student's t-test was used to assess the significance of differences between groups. Differences were considered statistically significant at $p < 0.05$.

The study complied with international bioethical requirements and the principles of the Declaration of Helsinki. The experimental protocol was approved by the Local Ethics Committee (Protocol No: 07/2026).

RESULTS

The experimental study revealed pronounced morphometric changes in the pulmonary vasculature of animals with modeled toxic hepatitis compared to the control group.

Analysis of vessel diameter showed significant differences between the groups. Experimental animals exhibited a noticeable decrease in the diameter of both arterioles and venules, indicating vascular spasm and microcirculatory impairment.

Table 1. Diameter of Pulmonary Vessels (μm)

Group	Arterioles (μm)	Venules (μm)
Control	48.2±2.1	62.5±3.4
Experiment	39.6±2.3*	55.1±2.9*

Note: Values are presented as M±SD— differences are statistically significant compared to the control group ($p < 0.05$).*

As shown in Table 1, the diameter of arterioles decreased from 48.2 ± 2.1 μm to 39.6 ± 2.3 μm, while the diameter of venules decreased from 62.5 ± 3.4 μm to 55.1 ± 2.9 μm ($p < 0.05$). These data indicate the formation of vasoconstrictive changes, likely associated with endothelial dysfunction and hypoxic processes in the lung tissue.

Further analysis demonstrated that the changes in vessel diameter were accompanied by significant wall thickening, a key sign of vascular remodeling.

Table 2. Vascular Wall Thickness (μm)

Group	Arterioles	Venules
Control	8.4 ± 0.6	6.2 ± 0.5
Experiment	12.7 ± 0.8*	9.5 ± 0.7*

Note: Data are presented as M ± SD — statistically significant differences compared to the control group ($p < 0.05$).*

As presented in Table 2, a significant increase in the vascular wall thickness of both arterioles and venules was observed in the experimental group ($p < 0.05$). Arteriolar wall thickening from 8.4 ± 0.6 μm to 12.7 ± 0.8 μm and venular thickening from 6.2 ± 0.5 μm to 9.5 ± 0.7 μm indicates the development of hypertrophic and fibrotic processes driven by the chronic damaging effect of the toxic agent.

The next stage of analysis involved the study of the vessel lumen area, which reflects the integral state of the vasculature and the degree of blood flow obstruction.

Table 3. Vessel Lumen Area (%)

Group	Arterioles	Venules
Control	100%	100%
Experiment	68.3%*	74.5%*

*Note: Indicators are expressed as a percentage relative to the control group (100%); * —* differences are statistically significant compared to the control ($p < 0.05$).*

According to Table 3, a significant reduction in the vessel lumen area was noted in the experimental group. The arteriolar lumen area decreased to 68.3%, and the venular area to 74.5% of control values ($p < 0.05$). These changes result from the combined effect of vascular narrowing and wall thickening.

Collectively, these results indicate the development of pronounced pulmonary vascular remodeling during toxic hepatitis. The reduction in vessel diameter, wall thickening, and decreased lumen area lead to increased vascular resistance, impaired microcirculation, and the formation of hypoxic states in the lung tissue.

DISCUSSION

The data obtained in this study indicate that toxic hepatitis exerts a profound systemic influence on the pulmonary vasculature, causing morphometric changes characteristic of vascular remodeling. These findings align with modern concepts viewing pulmonary vessels as a highly sensitive system responding to hypoxia, inflammation, and metabolic disturbances [1, 3].

The identified reduction in vessel diameter indicates the development of vasoconstrictive reactions and increased vascular tone. The narrowing of arterioles, which play a key role in regulating pulmonary blood flow, can lead to increased peripheral vascular resistance and impaired lung tissue perfusion. Similar mechanisms of vascular transformation have been described in pulmonary hypertension, where molecular signaling pathways, including HIF-1alpha-dependent processes, play a leading role [1, 23].

Equally significant is the identified thickening of the vascular wall, reflecting structural restructuring processes. These changes may be driven by smooth muscle cell hypertrophy, fibroblast activation, and increased synthesis of extracellular matrix components. Literature shows that vascular remodeling is accompanied by cellular proliferation and disruption of intercellular interactions, confirmed by 3D imaging of the vascular network [5, 8]. Inflammatory mediators and oxidative stress arising from toxic liver damage play a crucial role in these processes [6].

The reduction in lumen area in the experimental group is an integral indicator reflecting the combined impact of vasoconstriction and wall thickening. This confirms the presence of pronounced microcirculatory disturbances and indicates reduced blood supply efficiency to the lung tissue. Similar microcirculatory changes are described in chronic hypoxia and systemic diseases associated with vascular dysfunction [5, 10].

Notably, the most pronounced changes are observed in the arterial segment of the microcirculatory bed. This is consistent with literature emphasizing the primary role of arterioles in the formation of hemodynamic disturbances and the development of pulmonary hypertension [3, 19]. While the venous segment is also involved, the degree of its changes is less pronounced, possibly due to the functional characteristics of the venous system and its lower reactivity to vasoconstrictive influences.

The results correlate with studies indicating a close relationship between liver pathology and the pulmonary vascular system. Chronic liver diseases are known to cause systemic hemodynamic shifts, including endothelial dysfunction, impaired vascular tone, and

microcirculatory changes that can extend to the lungs [7, 9]. Furthermore, data on vascular restructuring in the liver during fibrosis confirm the systemic nature of angioarchitectonic changes [20].

Cellular elements of the vascular wall, specifically pericytes, play a significant role in regulating microcirculation and maintaining vascular stability. Their dysfunction may contribute to the progression of vascular remodeling and blood flow obstruction [22], supporting the view of vascular alterations as a multi-level process.

Attention should also be paid to data on systemic vascular changes after splenectomy, where pronounced wall restructuring and hemodynamic impairment are also noted [11, 13]. These results confirm that vascular alterations are systemic and can develop under various pathological conditions, including toxic liver injury.

Thus, the identified morphometric changes in pulmonary vessels during toxic hepatitis reflect a systemic pathological process involving vasoconstriction, wall thickening, and reduced lumen area. These alterations lead to microcirculatory failure, worsened lung tissue perfusion, and reduced gas exchange efficiency.

CONCLUSION

In conclusion, the results of this experimental study demonstrate that toxic hepatitis is accompanied by significant morphometric changes in the pulmonary vasculature. Specifically, animals in the experimental group exhibit reduced vessel diameter, vascular wall thickening, and a substantial reduction in lumen area.

These findings indicate the development of vascular remodeling and impaired pulmonary microcirculation, highlighting the systemic nature of the pathological process. The data confirm that liver injury affects not only the hepatobiliary system but also the pulmonary vascular network. Therefore, studying such changes is essential for a deeper understanding of the disease pathogenesis and for justifying a comprehensive approach to the diagnosis and prevention of its complications.

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