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Experimental Model of Pulmonary Hypertension in White Outbreed Rats

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Abstract: The morphological features of the lungs of rats are an experimental model in the case of studying the development of left ventricular pulmonary hypertension. Features of the innervation of the pulmonary veins of the roots of the lungs make the left lung of rats an object of study necessary for solving the problems of modern pulmonology, cardiology and morphology. Data obtained during experimental intervention indicate a valve-like action of the striated musculature of the pulmonary venous wall. The review of the literature is devoted to the structural features of the lungs of white rats.

Keywords: morphology, morphometry, pulmonary hypertension, lungs.

Relevance. Rats have lung structures that are different from human lungs. The structure of blood vessels in the lungs of rats must be studied in the case of a stress lung. Anatomical examination reveals the root of the diaphragmatic lobe, located in the caudal groove of the left lung. When studying the features of the syntopy and holotopy of the root and hilum of the left lung of mature white rats, the structural apparatus of the caudal sulcus was discovered, which is located for more than 11-17 mm on the medial surface of the diaphragmatic lobe of the left lung. The structural apparatus consists of the left caudal pulmonary vein, a groove on the surface of the diaphragmatic lobe of the left lung, the adventitia of the caudal bronchus, the visceral pleura, bronchial nerves and blood vessels, and encapsulated receptors. The presence of cardiomyocytes in intrapulmonary veins in rats supports the hypothesis of a rhythmic, valve-like action of the striated musculature of the pulmonary venous wall during systole and a possible role in pulmonary circulation. Given the relevance of the pathology of the respiratory system, it becomes necessary to search for and correct an experimental model of pulmonary hypertension and stress lung. Outbred albino rats (Rattus norvegicus) are one of the main stress models. The peculiarities of the innervation of the lungs of rats are confusing [5]. In them, autonomic efferent (sympathetic and parasympathetic) perivascular axons barely extend beyond the hilum of the lungs, whereas in humans this innervation extends to small intrapulmonary vessels. The peripheral parts of the lungs of rats are characterized by a very low number or even the absence of nerve endings. The proximal bronchi, proximal pulmonary arteries, and proximal pulmonary veins of rats contain a large number of adrenergic and cholinergic nerve endings. In the distal bronchi, distal pulmonary arteries, and distal pulmonary veins of rats, the number of adrenergic and cholinergic nerve endings is significantly reduced [2, 3, 3, 4]. The predominant innervation of the right lung was found in rats; it has a higher density of nerve endings than in the left lung [58]. Violation of blood oxygenation processes in the pulmonary circulation is closely related to the body's reflex response to hypoxia, which leads to pulmonary hypertension [4]. When choosing other animals as an experimental model, the problem of morphological diagnostics of pulmonary arteries and pulmonary veins arises. So far, it is difficult to distinguish during microscopy the differences between pulmonary veins and pulmonary arteries of the muscular

and mixed type in humans and a number of other animals [7]. In the small distal pulmonary arteries, the lamina musculature may thin and eventually disappear. The structure of small intrapulmonary veins shows some similarity with small arteries: thin intima and smooth muscle tissue contained in large diameter veins, and adventitium, which includes vasa vasorum, nerves, and ligaments of collagen or elastic fibers [5]. Lungs of rats have specific features [1, 2]. In the right lung of white rats there are four lobes separated by furrows. The right lung of rats is formed by the apical, cardiac, diaphragmatic, and accessory lobes. In the left lung of rats there is one lobe in which there is no interlobar groove. You suggested that the left lung of rats is divided into segments [13]. For experimental evaluation of the bronchial tree of rats, other authors propose a histological classification of the respiratory tract in rats: 1) trachea and extrapulmonary bronchi; 2) intrapulmonary bronchi (diameter more than 500 microns); bronchioles (diameter less than 500 μm) [4]. The disadvantage of this classification is that it does not quite reliably reflect the function of the distal parts of the airways of the lungs of rats. Other authors distinguish terminal bronchioles and preterminal bronchioles in the lungs of rats with a bronchiole lumen diameter of less than 250 μm [3, 19].

In the study of the anatomy of rats, academician A.D. Nozdrachev [13] found that many smaller branches branch out from each lobar bronchus - segmental bronchi, which add air to the whole single broncho-pulmonary segment. The branching of the vessels repeats the branching of the bronchi, the arteries are closely adjacent to the bronchi from above, the veins pass at some distance from below. Each pulmonary artery is located on the wall of the bronchus and, according to its division, gives a branch to the lung parenchyma. The pulmonary veins originate one from each lobe of the lung - one vein from the left lung and four from the right. Each of these veins is formed by the fusion of vessels emerging from the lobules of the lung. In their course from the lobes of the lung, the veins lie anterior and dorsal to the bronchi, while the pulmonary arteries are located ventral and behind the bronchi [4, 5, 13]. The hilum is the main channel through which the arteries and their paired airways pass through the center of the root and the hilus of the lungs to reach the pleural surface. Broncho vascular bundles run along this axial path. In cows, pigs, and sheep, the bronchovascular bundle in the lungs includes the pulmonary veins. In contrast, in smaller mammals—monkeys, dogs, cats, rabbits, guinea pigs, and rats—the pulmonary veins follow independently of the airway bundle and artery [8, 7]. In the lungs of horses and humans, there is a mixed picture of the structure of the bronchovascular bundle: in the distal part of the lungs, the pulmonary arteries, airways, and veins form a common bundle, while the proximal pulmonary veins arise from the bundle of airways and arteries [46]. Lymphatic vessels lie within the adventitial sheaths of the bronchovascular bundles. The caudal mediastinal lymph nodes that collect lymph from the lungs of rats are located between the esophagus and the aorta, adjacent to the esophagus on the right side, and on the left, next to the cranial vena cava. The right caudal mediastinal and left lymph nodes drain the pleural space and lung, the base of the heart and the thoracic part of the esophagus, chest organs and thymus [1, 2, 3, 5]. During a surgical operation on the lungs of rats, the left pulmonary vein, due to its anterior position, was the first structure to be dissected. Two segmental left pulmonary veins were observed in the left lung of rats. The left superior pulmonary vein crossed anteriorly with the left main bronchus. The left inferior pulmonary vein forms a long venous trunk [6, 7]. According to the data presented in our works [4, 5], when leaving the lung, the pulmonary veins penetrate into the left auricle of the left atrium. The right side pulmonary veins run dorsal to the left cranial vena cava. On the left side, the pulmonary veins are crossed by the bend of the unpaired vein, just at the place where the latter flows into the left cranial vena cava. In their course from the lobes of the lung, the veins lie anterior and ventral to the bronchi, while the pulmonary arteries are located dorsal and posterior to the bronchi. There is a hypothesis that two lobes are formed in the left lung of rats during embryonic development [12]. An anatomical study revealed that the left lung in white rats did not have extended grooves on its costal surface. On the medial surface of the left lung, two deep furrows (but not through cracks) of different lengths are determined. They depart from the gate of the lung at different levels relative to the left main bronchus: 1) the

cranial groove is transverse, soon becomes superficial and practically “disappears”, it corresponds to a deep notch on the ventral edge of the lung; 2) caudal groove - oblique, at first descending to the caudal edge of the lung, deep, parallel to it and more superficial, but ends with a pronounced notch on the ventral edge of the lung. There are problems with the anatomical terminology for the details of the rat lungs. In the right lung in rats, the lobes of the lungs were named: upper, cardiac, diaphragmatic, accessory. In view of this, the term “diaphragmatic lobe” of the left lung of rats was proposed [3]. V.M. Petrenko suggests the terms “cranial” and “caudal” (diaphragmatic) lobes of the left lung. Given the absence of an interlobar sulcus in the left lung, the necessity of this hypothesis remains unknown. There is evidence that deep furrows divide the right lung of the white rat into at least 5 lobes, and the left lung into 3 "hidden" lobes. The distribution of the branches of the main bronchi in the lungs needs to be further investigated to justify the division of the lungs into certain lobes. The “hidden” lobes of the left lung probably fused under the pressure of the right lung and the heart, which led to the “flattening” of the left lung in the transverse direction [4–6]. V.M. Petrenko suggested that there is a mass-gravitational influence of the environment on the phylogenesis of the lungs, leading to the appearance of an abdominal somatotype (a special variant of the human morphic somatotype brachy). The voluminous intestines, in combination with the liver, support the diaphragm, on which the heart is flattened. In turn, pressure is exerted on the neighboring lungs - these three organs determine the overall appearance of the individual's chest cavity. The relative enlargement of the liver (guinea pig → rat), especially its dorsal sections (rat), increases the pressure on both the diaphragm and the underlying intestine, further complicating the picture of organogenesis [1].

Elastic fibers are short, relatively thin and interspersed with collagen and smooth muscle cells. Large elastic pulmonary arteries, in which the middle shell consists of several layers of an elastic membrane and smooth muscle cells, gradually continue into smaller muscular arteries. As the diameter decreases, the arteries become more clearly defined by one inner and one outer elastic membrane. Human and rat pulmonary arteries less than 1 mm in diameter contain single internal and external membranes [2]. In contrast to the oval or elliptical shape of endothelial cell nuclei in the pulmonary artery, in the pulmonary veins, the cell nuclei are polygonal or round. In humans and dogs, large muscular pulmonary veins and small pulmonary veins have an indistinct or absent internal elastic membrane [3, 4]. Pulmonary veins contain more extracellular matrix and less smooth muscle than pulmonary arteries [9]. In rats, the frequency with which the muscular arteries are close to the respiratory bronchioles is significantly less, ranging from 4-10%. Muscular arteries can be found distal near the alveolar lung wall in dogs, rabbits, and rats [3, 8]. The extrapulmonary veins differ from the veins of the systemic circulation. They flow into the left atrium and also contain cardiomyocytes. Intrapulmonary veins of rats are characterized by the inclusion of islets of tissue formed by cardiomyocytes. Cardiomyocyte cells cover the walls of intrapulmonary veins [11]. When using scanning electron microscopy of vascular casts, in pulmonary veins with a diameter of 20–50 μm in rats and mice, sphincter-like structures were found, as in cattle [5, 6]. Taking into account the literature data [6], it is logical to assume that the smallest diameter of an intralobular venule is from 20 to 50 μm. Rats have 11–12 branches of arteries and veins [7]. In a functional study of the pulmonary veins of rats, a number of researchers describe a bifurcation of the left pulmonary vein in the hilum of the left lung [4, 3, 7]. The myocardial plate of the pulmonary veins of the rat has a sufficient length, up to bifurcations of the second order and intrapulmonary areas [9–11]. It is typical for rats and mice that the venous section breaks up into very small veins [5]. Functional studies of ion channel expression and pulmonary vein electrophysiology indicate a significant contribution of cardiomyocytes to rat pulmonary vein tone [9, 3]. In isolated intrapulmonary veins of rats, the layer of cardiomyocytes makes a significant contribution to electrical activity. Activation of the pulmonary veins of the myocardium can lead to the spread of electrical activity to the myocardium [1, 8–10]. An electrophysiological study of the functional state of the pulmonary veins can be reliably measured only under in vitro conditions, in a culture of perfused cell preparations of the pulmonary vein [1, 11]. According to the most common concept at present,

ectopic activity in the myocardial lining (sleeves) of the pulmonary veins, which interacts with electrical activity in the atria, is the cause of atrial fibrillation. The myocardial tissue in the pulmonary veins differs from the atrial one and has a number of features of the morphological structure and bioelectrical activity. The myocardial plates of the pulmonary veins, both under experimental conditions and in vivo, are the site of localization of foci of trigger activity, abnormal automaticity, and circulation of excitation, i.e., factors leading to various types of arrhythmias, in particular, to atrial fibrillation. The change in bioelectrical activity in the pulmonary vein myocardium under the action of pharmacological agents is a critical, central element of the mechanism for initiating atrial fibrillation, as well as its prevention. There are several methods for detecting in vivo and in vitro, predicting antiarrhythmic activity. These are models of calcium chloride and barium chloride arrhythmias, adrenaline and aconitine models of arrhythmias. The essence of these methods is the administration of high doses of calcium, barium, aconitine, ouabain, or strophanthin to anesthetized or awake animals [2, 3]. The adrenaline model of arrhythmia has a similar nature, differing from the previous approach only in the direct administration of adrenaline [8]. Differences from the known data on the structure of rats have been established, which indicate that the pulmonary veins run separately from the bronchovascular bundle [3, 7]. The participation of the caudal vein in the formation of the bronchovascular bundle in the root of the diaphragmatic lobe of the left lung in rats, which is then structurally separated from the adventitium of the distal generations of the bronchi, has been found [4, 5]. Generations of intrapulmonary bronchi form preterminal and terminal bronchioles, in which the lumen diameter is less than 270–250 μm [3, 19]. This confirms the data that in rats the diameter of the lumen of the distal bronchi is less than 270–250 μm [5]. In the hilum of the lungs of rats after cutting off the root, the following are found: caudal and cranial bronchi, lobar caudal and cranial veins, pulmonary artery, nerves, etc. This confirms the data that there are caudal and cranial bronchi of generation 121 and 122 in the hilum and root of the left lung [5]. It draws attention to the fact that in this organ there is no interlobar furrow. This casts doubt on the hypothesis of the existence of "hidden lobes" in the left lung of rats, separated by shallow interlobar grooves [12, 14–17]. On the medial surface of the left lung in rats, there are caudal and cranial grooves running from the lung root to the diaphragmatic and cranial margins [5, 13–16]. At the bottom of the caudal groove under the caudal vein are the caudal bronchus and pulmonary artery, which indicates the existence of the diaphragmatic lobe. The study of syntopy and holotopy of the root and hilum of the left lung revealed the structural apparatus of the caudal sulcus, which is located on the medial surface of the diaphragmatic lobe of the left lung in sexually mature albino rats [4, 5]. The structural apparatus consists of the left caudal pulmonary vein, a groove on the surface of the diaphragmatic lobe of the left lung, the adventitial membrane of the caudal bronchus, the visceral pleura, bronchial nerves and blood vessels, and encapsulated receptors. Using the immunohistochemical method (reaction to synaptophysin), the pulmonary vein of adult male rats was studied. It has been established that the wall of its intrapulmonary trunk has a unique structure. Throughout the vein, cardiac muscle fibers are richly innervated. Efferent synaptophysin-positive endings of the terminal plexus were found in close association with cardiomyocytes, capillaries of the median membrane in the area of the pulmonary vein orifice, and adventitia vasa vasorum [2,4]. This indicates a significant role of calcium dependent processes in the regulation of the function of nerve endings in the pulmonary myocardium. A histochemical study revealed a significant trend that reflects the high content of calcium cations in the pulmonary veins of rats [2, 6]. A functional study of the pulmonary veins of rats describes a bifurcation of the left pulmonary vein in the hilum of the left lung [3, 6, 7]. The extrapulmonary location of the caudal vein of the phrenic lobe of the left lung of albino white rats draws attention [6]. The role of the diaphragmatic lobe of the left lung of rats as a blood depot, which regulates venous return of blood to the left atrium, has been established [3, 4, 6]. Hyperemia of the lungs is explained by the peculiarity of the mechanism of contraction of cardiomyocytes in the pulmonary veins of rats. The physiological direction of action potential propagation in the pulmonary veins of rats is towards the lung. This supports the hypothesis of a rhythmic, valve-like action of the striated musculature of the pulmonary venous wall during

systole and a possible role in pulmonary circulation capacity [5]. In experimental animals, there is a complex mechanism for the development of pulmonary congestion and pulmonary hypertension [3, 4]. Susceptibility to chronic proliferative pulmonary hypertension in response to chronic alveolar hypoxia is most pronounced in species that have reduced or absent adrenergic innervation of the pulmonary arteries. Rats develop severe proliferative pulmonary hypertension in response to prolonged alveolar hypoxia. It has been suggested that increased adrenergic activity and innervation density cause hypertrophy of the blood vessels in hypertensive animals. Adrenergic nerves have a protective effect on the pulmonary vessels [4]. Therefore, the effectiveness of the study of rat lungs as an experimental model of pulmonary hypertension and stress has now been proven.

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