

Radiofrequency denervation of the pulmonary artery trunk in the modulation of pulmonary hypertension in cardiovascular pathology. Experimental study

Ilyin M.V.¹, Moskvichev E.V.^{1,2}, Kozlov V.A.¹, Dragunov A.G.³,
Dragunova M.V.⁴, Romanov V.S.⁵

¹ Chuvash State University, Cheboksary, Russia.

² Republican Clinical Oncology Dispensary, Cheboksary, Russia.

³ "Angio Lab" LLC (innovative medical company), Cheboksary, Russia.

⁴ Republican Cardiology Dispensary, Cheboksary, Russia.

⁵ Republican Bureau of Forensic Medical Examination, Cheboksary, Russia.

AUTHORS

Mikhail V. Ilyin, Senior Lecturer, Department of Normal and Topographic Anatomy with Operative Surgery, I.N. Ulyanov Chuvash State University, Cheboksary, Russia. ORCID: 0009-0009-3820-7166

Evgeny V. Moskvichev, MD, PhD, Professor, Department of Normal and Topographic Anatomy with Operative Surgery, Chuvash State University; Head of the Pathology Department, Republican Clinical Oncology Dispensary, Cheboksary, Russia. ORCID: 0000-0002-2850-5487

Vadim A. Kozlov, MD, PhD, Dr. in Biological Sciences, Professor, Department of Medical Biology with a Course in Microbiology and Virology, Chuvash State University; Leading Researcher, Institute for Advanced Medical Training, Cheboksary, Russia. ORCID: 0000-0001-7488-1240

Andrey G. Dragunov, MD, PhD, CEO, "Angio Lab" LLC (innovative medical company), Cheboksary, Russia. ORCID: 0000-0002-9949-2281

Marina V. Dragunova, Cardiologist, Republican Cardiology Dispensary, Cheboksary, Russia. ORCID: 0009-0000-3489-0169

Vladimir S. Romanov, Head of Cheboksary Interdistrict Pathology Department No. 1, Republican Bureau of Forensic Medical Examination, Cheboksary, Russia. ORCID: 0009-0002-8117-7336

In recent years, radiofrequency ablation (RFA) of the pulmonary artery (PA) trunk has been successfully applied in patients with cardiac pathology complicated by severe pulmonary hypertension (PH), demonstrating high effectiveness in improving quality of life and prognosis. At the same time, the question of objectifying the mechanisms of action of PA trunk RFA and its hemodynamic/clinical efficacy remains under discussion, which served as the basis for this experimental study.

The aim of the study is to substantiate the effectiveness of PA trunk RFA in reducing pulmonary hypertension using immunohistochemical assessment of the completeness of sympathetic denervation by determining the S-100 marker under experimental conditions.

Methods. The study included 30 pulmonary artery trunks obtained from individuals who died of non-cardiac causes, aged 31 to 65 years. Immunohistochemical staining for the S-100 protein was performed.

Results. In sections of pulmonary artery trunks subjected to RFA, nerve fibers did not stain for S-100, which indicates the destruction of autonomic nerve fibers in the pulmonary trunk.

Conclusion. Immunohistochemical staining for S-100 is a valid method for verifying irreversible thermal damage to autonomic nerve fibers in the pulmonary artery trunk as a result of RFA.

Keywords: radiofrequency ablation, pulmonary hypertension, autonomic nerve fibers, pulmonary trunk, immunohistochemistry, S-100.

Conflict of interests: none declared.

Received: 28.11.2025

Accepted: 04.02.2026



For citation: Ilyin M.V., Moskvichev E.V., Kozlov V.A. et al. Radiofrequency denervation of the pulmonary artery trunk in the modulation of pulmonary hypertension in cardiovascular pathology. Experimental study. 2026; 49(14): 34-39. DOI: 10.24412/2311-1623-2026-49-43-49

Introduction

Cardiovascular diseases continue to rank among the leading causes of mortality worldwide. According to the Ministry of Health of the Russian Federation, in 2024 approximately 45% of all deaths in the country were associated with heart and vascular diseases [1]. According to the World Health Organization, cardiovascular diseases claim the lives of nearly 17.9 million people annually [1]. The prevalence of mitral valve disease reaches 8%, and its numerous complications require an individualized surgical approach [2–4]. Pulmonary hypertension (PH) often accompanies many cardiac and pulmonary diseases, as well as autoimmune disorders [3]. In PH, there is a progressive increase in pressure within the pulmonary artery system, leading to right ventricular heart failure and premature death [4]. The pathogenesis of the disease is associated with endothelial dysfunction, characterized by increased production of vasoconstrictors (thromboxane, endothelin-1) and decreased production of vasodilators (NO, prostacyclin), resulting in vascular wall remodeling manifested by reduced elasticity, vascular obliteration, and reduction of the pulmonary vascular bed [2].

In recent years, in a number of cardiac surgery centers in Russia and abroad, radiofrequency denervation (RFD) of the pulmonary artery (PA) trunk has

been performed simultaneously with surgical correction of acquired mitral valve disease [3, 4]. It has been shown that this procedure allows for an additional reduction in mean pulmonary artery pressure [4] compared to isolated correction of mitral valve disease, thereby improving long-term prognosis in this severe category of cardiac surgical patients [5, 6]. In addition to its effectiveness, RFA of the PA trunk has demonstrated safety in clinical studies [7–9]. Besides the minimally invasive catheter-based endovascular RFA procedure, it is often performed during surgical correction of mitral valve disease in patients complicated by atrial fibrillation. The essence of the method lies in creating circular sympathetic denervation, i.e., RFA of ganglionated plexuses of the PA trunk and its orifices, using a specialized clamp-destruction device [10–11]. An informative method for assessing the degree of PA denervation and, consequently, the effectiveness of the procedure is immunohistochemical analysis using polyclonal antibodies to the S-100 protein. The S-100 protein is a low-molecular-weight calcium-binding protein that serves as a sensitive marker of nerve tissue damage [8].

As a result of RFA, structural changes occur in the pulmonary artery tissues, including the sympathetic

fibers located on its surface that exert a vasoconstrictive effect on intrapulmonary vessels [2]. Complete capture and irreversible thermal damage of sympathetic fibers may lead to total desympathization of the pulmonary vascular bed and a sustained reduction in pulmonary artery pressure in the postoperative period.

The aim of the study is to substantiate the effectiveness of PA trunk RFA in reducing pulmonary hypertension through immunohistochemical assessment of the completeness of sympathetic denervation by determining the S-100 marker under experimental conditions.

Methods. A total of 30 pulmonary artery trunks obtained during planned autopsies from individuals who died of non-cardiac causes, aged 31 to 65 years, were studied. The material was collected no later than 6 hours after death.

For PA denervation, a radiofrequency generator ("Angio Lab") operating at a frequency of 440 kHz was used, with adjustable exposure time ranging from a few seconds to several minutes and power output from 5 to 120 W. In the experiment, a power setting of 10 W was applied until a circular coagulation line appeared in the RFA area, indicating complete visual damage to the entire wall of the PA trunk. To study the topography of autonomic nerve fibers, five randomly selected pulmonary artery trunks were used as controls for comparison with PA trunks treated with RFA. Samples of pulmonary artery trunks were fixed in 10% neutral buffered formalin, and paraffin blocks were prepared according to a standard protocol. Immunohistochemical staining of the PA wall for the S-100 protein was performed using a Leica Bond MAX immunostainer and polyclonal antibodies to S-100, which provide high staining sensitivity. Nuclear counterstaining was performed with hematoxylin and eosin [9]. Analysis of the obtained histological material was carried out using a Leica DM 4000 microscope with Leica Application Suite 3.8 morphometry.

Statistical analysis

For primary data processing, systematization, and summarization, methods of descriptive and variation statistics were used. As a quantitative measure, the relative area (μm^2) of nerve fibers (S_{rel}) was used, defined as the ratio of the mean area of stained nerve fibers within the field of view to the total area of the field of view. For each pulmonary artery trunk, 5 sec-

tions were examined with 10 fields of view each, and the arithmetic mean value was calculated. The data are presented as median values (Me) with $\pm 95\%$ confidence interval. Differences between two independent groups were determined using a nonparametric method with the Mann-Whitney U test. Differences between groups were considered statistically significant at $p < 0.05$.

Results

In immunohistochemical examination for the S-100 protein, intact autonomic nerve fibers within the nerve trunk stain intensely in sepia shades (Fig. 1a). They appear as oval structures located adjacent to the vasa vasorum at the boundary between the adipose tissue surrounding the pulmonary trunk and its wall. The membranes of adipocytes and the fibrillar structures of the vasa vasorum and the pulmonary trunk stain in sepia tones less intensely than the autonomic nerve trunks.

Pulmonary artery trunk segments subjected to RFD do not demonstrate immunohistochemical staining for the S-100 protein (Fig. 1b). The sections reveal basophilically stained cell nuclei, as well as shadow-like remnants of the vasa vasorum and adjacent autonomic nerve trunks. The fibrillar structure of the walls of the vasa vasorum and the pulmonary trunk is not visualized. Circular areas of expanded empty space are observed around the nerve trunks, apparently formed by water vapor during the RFA process. A single nerve fiber is identified within the structure of the vasa vasorum in the adventitial layer of the pulmonary artery (Fig. 1b).

The observed changes are similar to those seen in thermal injury. The absence of characteristic immunohistochemical staining for the S-100 protein is likely associated with thermal coagulation of proteins in the RFD zone of the pulmonary artery. It is evident that proteins lose both their native structure and antigenic properties under these conditions, which prevents staining with antibodies to the marker protein [8].

A comparative assessment of the RFD results revealed a statistically significant difference in the Srel parameter between the left lateral margin of the pulmonary trunk and the anteroposterior wall of the pulmonary trunk (Table 1): 5.72% and 0.99%, respectively ($p < 0.05$).

It is known that the extracardiac plexus of the heart is involved in the innervation of other organs of the

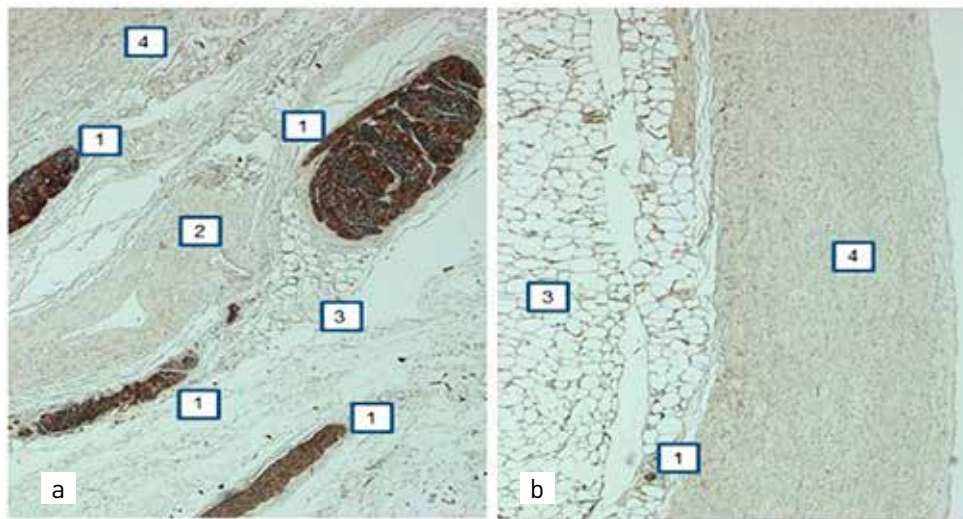


Fig. 1. Anterior wall of the pulmonary trunk. Immunohistochemical staining, magnification $\times 200$:

a) 1 – nerve fiber, 2 – vasa vasorum, 3 – adipose tissue, 4 – wall of the pulmonary trunk,

b) 1 – a single nerve fiber within the structure of the vasa vasorum in the adventitial layer of the pulmonary artery, 3 – adipose tissue, 4 – wall of the pulmonary trunk

Table 1. Relative area of stained nerve trunks (S_{rel})

Parameter	Left lateral margin of the pulmonary trunk	Anterior and posterior walls of the pulmonary trunk
S_{rel}	5.72 % (95 % CI 4.27–8.95)	0.99 % (95 % CI 0.48–0.93)

thoracic cavity, including the pulmonary trunk, PA, and lungs. The innervation of the heart, aorta, and pulmonary trunk is carried out by branches of the cervical sympathetic ganglia. Two cardiac plexuses are distinguished: superficial and deep. The superficial cardiac plexus is located between the aortic arch and the pulmonary trunk. It receives cardiac nerves from the left superior cervical sympathetic ganglion and the left superior cervical cardiac branch of the vagus nerve. The deep cardiac plexus is located posterior to the aortic arch, adjacent to the tracheal bifurcation. It is formed by all other branches of the cervical sympathetic ganglia: the right superior cervical, the middle, and the stellate ganglia.

In this study, the following cardiac plexuses are considered, which cover the regions of the pulmonary trunk subjected to RFA 1) the anterior left plexus, which descends from the left surface of the pulmonary trunk onto the anterior wall of the left ventricle; 2) the anterior right plexus, which descends from the right surface of the pulmonary trunk and the ascending aorta onto the posterior wall of the right ventricle.

Thus, according to the above data, sympathetic innervation of the selected area is provided by branches

of the superficial cardiac plexus, which exert a vasoconstrictive effect on the pulmonary vessels and are located along the lateral surfaces of the pulmonary trunk. In addition, localized RFA applied to the lateral walls of the pulmonary trunk, closer to the site of bifurcation, is unlikely to have a significant effect on bronchial smooth muscle tone, since parasympathetic innervation of the lungs is provided by the parasympathetic plexus (branches of the vagus nerve) located at the pulmonary hilum.

Discussion

It should be noted that one of the promising directions in endovascular surgery is the use of RFA technology for interventional procedures in various cardiovascular diseases. This includes well-established catheter ablation for severe cardiac arrhythmias [12]. In addition, renal sympathetic denervation has long been used in clinical practice for patients with refractory arterial hypertension, demonstrating good antihypertensive efficacy and improved prognosis [13].

In this context, RFA of the pulmonary trunk and the PA orifices has also demonstrated high efficacy and safety in patients with severe PH undergoing surgical correction of valvular heart disease, including cases complicated by atrial fibrillation [2, 11]. According to other researchers, the efficacy and safety of RFD of the pulmonary trunk and PA orifices in severe PH have been confirmed based on histological examina-

tion of autopsy material [9]. This method represents an effective and safe approach for denervation of sympathetic plexuses located in the adventitial layer of the pulmonary artery. Histological examination of the adventitia of the pulmonary trunk and PA orifices subjected to circular RFA confirms the effectiveness of RFD, demonstrated by a 16% reduction in the mean specific area of nerve endings compared to tissues not exposed to the procedure. It has been shown that RFA of sympathetic nerve fibers of the pulmonary trunk enables effective and long-term control of pulmonary artery pressure in patients with valvular heart disease [2, 3].

In the present study, the effectiveness of RFD is described using quantitative analysis of the relative area of stained nerve endings. This method helps to avoid subjectivity in assessing the degree of damage induced by PA RFA. The use of the relative area of stained nerve fibers as a parameter reduces morphometric measurement errors associated with tissue changes during fixation and paraffin embedding. As a result of RFD, pulmonary artery trunk segments subjected to the procedure do not

exhibit immunohistochemical staining for the S-100 protein. The described changes in the pulmonary artery correspond to the pattern of thermal injury, indicating a persistent effect of sympathetic denervation.

Conclusion

Immunohistochemical staining for the S-100 protein is a reliable method for verifying irreversible thermal damage to autonomic nerve fibers in the pulmonary artery trunk as a result of PA RFD. This approach can be used to assess the effectiveness of PA denervation. The identified histotopographic patterns of autonomic nerve fibers in the adventitial layer of the human pulmonary artery should be taken into account when performing surgical interventions, including PA RFD in clinical practice.

Thus, immunohistochemical examination for the S-100 protein is an informative tool for evaluating the effectiveness of PA trunk RFD and thereby confirms the pathophysiological mechanism of this procedure.

Conflict of interests: none declared.

References

- Oganov RG, Shalnova SA, Maslennikova GYa Epidemiology and prevention of cardiovascular diseases. *Cardiology news, opinions, training*. 2025.13 (1): 73-85. Russian.
- Trofimov NA, Medvedev AP, Nikolsky AV et al. Denervation of pulmonary arteries in patients with mitral valve defects complicated by atrial fibrillation and high pulmonary hypertension. *Modern technologies in medicine*. 2019; 11: 95–105. Russian. DOI: 10.17691/stm2019.11.4.11
- Korobchenko LE, Goncharova NS, Condori Leandro H.I. et al. Pulmonary artery denervation in pulmonary hypertension: a systematic review and meta-analysis of clinical trials. *Arterial Hypertension*. 2021;27(6):628–641. Russian. DOI: 10.18705/1607-419X-2021-27-6-628-641
- Lee F, Mielniczuk LM Pulmonary Hypertension Due to Left Heart Disease: A Practical Approach to Diagnosis and Management. *Can J Cardiol*. 2021; 37:572. DOI: 10.1016/j.cjca.2020.11.003
- Rudenko VA, Feshchenko DA, Shanoyan AS Endovascular methods of pulmonary artery denervation in the treatment of patients with pulmonary hypertension: textbook. manual; Ed. by Drapkina O.M. Moscow: Federal State Budgetary Institution "National Medical Research Center for Therapy and Prevention of Medicine of the Ministry of Health of the Russian Federation", 2020. 66 p. Russian.
- Condori Leandro HI, Vakhrushev AD, Goncharova NS et al. Stimulation Mapping of the Pulmonary Artery for Denervation Procedures: An Experimental Study. *J Cardiovasc Transl Res*. 2021; 14 (3): 546–555. DOI: 10.1007/s12265-020-10079-4
- Feshchenko DA, Rudenko BA, Shanoyan AS et al. Pulmonary Artery Denervation for Pulmonary Hypertension: stages of development and clinical experience. *Russian Journal of Cardiology*. 2019. 24(12): 162–168. Russian. DOI: 10.15829/1560-4071-2019-12-162-168
- Trofimov NA, Rodionov AL, Egorov DV et al. Histological justification for the need of radiofrequency ablation of pulmonary arteries in patients with high-grade secondary pulmonary hypertension. *Modern technologies in medicine*. 2021. 13(6): 56–64. Russian. DOI: 10.17691/stm2021.13.6.06
- Vasiltseva OYa, Uranov AE, Edemsky AG et al. Treatment of patients with chronic thromboembolic pulmonary hypertension. *Clinical Medicine*. 2023; 101 (7–8): 361–367. Russian. DOI: 10.30629/0023-2149-2023-101-7-8-361-367
- Chernyavsky AM, Edemsky AG, Novikova NV et al. Use of radiofrequency ablation of the pulmonary artery in the treatment of residual pulmonary hypertension after pulmonary endarterectomy. *Cardiology*. 2018;58(4):15–21. Russian. DOI: 10.18087/cardio.2018.4.10105



11. Lednev PV, Belov YuV, Komarov RN. et al. Results of radiofrequency ablation of the pulmonary vein orifices as a method for preventing postoperative atrial fibrillation. *Surgery. Journal im. N.I. Pirogov.* 2017;(6):16-21. Russian. DOI:10.17116/hirurgia2017616-21
12. Sholin IYu, Ustinov DD, Kiselev DG et al. Radiofrequency ablation in the treatment of recurrent ventricular tachycardias using ECMO: clinical observations. *Obschchaya reanimatologiya.* 2026;22(1): 56–63. Russian. DOI: 10.15360/1813-9779-2026-1-2670
13. Mahfoud F, Kandzari DE, Kario. K. et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet.* 2022; 399:1401-1410. DOI: 10.1016/S0140-6736(22)00455-X