УДК 612.135:612.145:612.148:612.089.6:615.224:616-005.755
DOI: https://doi.org/10.17816/MAJ96368

THE IMPACT OF NEBIVOLOL, CARVEDILOL AND PROPRANOLOL ON PULMONARY MICROHEMODYNAMICS IN CASE OF EXPERIMENTAL PULMONARY THROMBOEMBOLISM IN RABBITS

Vadim I. Evlakhov[1, 2], Ilya Z. Poyassov[1, 3], Tatiana P. Berezina[1]

[1] Institute of Experimental Medicine, Saint Petersburg, Russia;
[2] Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia;
[3] Saint-Petersburg State University of Aerospace Instrumentation, Saint Petersburg, Russia

For citation: Evlakhov VI, Poyassov IZ, Berezina TP. The impact of nebivolol, carvedilol and propranolol on pulmonary microhemodynamics in case of experimental pulmonary thromboembolism in rabbits. *Medical Academic Journal.* 2022;22(1):17–27. DOI: https://doi.org/10.17816/MAJ96368

Received: 13.01.2022 Accepted: 18.03.2022 Published: 30.03.2022

BACKGROUND: Beta-adrenoblockers nebivolol, carvedilol and propranolol are used in clinical cardiology for the treatment of patients with ischemic heart disease. Pulmonary thromboembolism can develop in such patients. However, its unknown, what will be the pulmonary microcirculatory changes in case of pulmonary thromboembolism after pretreatment with beta-blockers.

AIM: The comparative analysis of the pulmonary microhemodynamics changes following experimental pulmonary thromboembolism in rabbits after pretreatment with nebovolol, carvedilol and propranolol.

MATERIAL AND METHODS: In 35 isolated perfused rabbit lungs we investigated the changes of pulmonary microcirculation in case of experimental pulmonary thromboembolism after pretreatment with β_1-blocker — nebivolol, combined blocker of α_1- and $\beta_{1,2}$-adrenoceptors — carvedilol, and blocker of $\beta_{1,2}$-adrenoceptors propranolol.

RESULTS: After administration of $\beta_{1,2}$-adrenoceptors blocker — propranolol and β_1-blocker — nebivolol the most of the pulmonary microcirculatory parameters increased. Combined α_1-, $\beta_{1,2}$-blocker carvedilol caused mainly vasodilatory effects of the pulmonary arterial vessels, however, the pulmonary venous resistance increased. Pulmonary thromboembolism after pretreatment with beta-blockers caused pronounced increase of pulmonary artery pressure, precapillary and pulmonary vascular resistance. In that case after pretreatment with carvedilol capillary filtration coefficient was increased two times more than after propranolol administration; after pretreatment with nebivolol capillary filtration coefficient increased less, than after propranolol administration.

CONCLUSIONS: Acute pulmonary embolism caused less pronounced increasing of capillary filtration coefficient in case of nebivolol administration, than after pretreatment with carvedilol and propranolol.

Keywords: pulmonary thromboembolism; pulmonary microhemodynamics; capillary filtration coefficient; nebivolol; carvedilol; propranolol.

ВЛИЯНИЕ НЕБИВОЛОЛА, КАРВЕДИЛОЛА И ПРОПРАНОЛОЛА НА МИКРОЦИРКУЛЯЦИЮ ЛЕГКИХ В УСЛОВИЯХ ЭКСПЕРИМЕНТАЛЬНОЙ ТРОМБОЭМБОЛИИ ЛЕГОЧНОЙ АРТЕРИИ У КРОЛИКОВ

В.И. Евлахов[1, 2], И.З. Поясов[1, 3], Т.П. Березина[1]

[1] Институт экспериментальной медицины, Санкт-Петербург, Россия;
[2] Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова, Санкт-Петербург, Россия;
[3] Санкт-Петербургский государственный университет аэрокосмического приборостроения, Санкт-Петербург, Россия

Для цитирования: Евлахов В.И., Поясов И.З., Березина Т.П. Влияние небиволола, карведилола и пропранолола на микроциркуляцию легких в условиях экспериментальной тромбоэмболии легочной артерии у кроликов // Медицинский академический журнал. 2022. Т. 22. № 1. С. 17–27. DOI: https://doi.org/10.17816/MAJ96368

Рукопись получена: 13.01.2022 Рукопись одобрена: 18.03.2022 Опубликована: 30.03.2022

Обоснование. Бета-блокаторы небиволол, карведилол и пропранолол применяются в клинической кардиологии для лечения больных ишемической болезнью сердца. У таких пациентов может возникать тромбоэмболия легочной артерии. Однако неизвестно, каковы будут изменения микроциркуляции легких в случае легочной тромбоэмболии после применения бета-блокаторов.

Цель — проведение сравнительного анализа изменений микрогемодинамики легких в условиях экспериментальной тромбоэмболии легочной артерии у кроликов после применения небиволола, карведилола и пропранолола.

Материалы и методы. На 35 изолированных перфузируемых легких кроликов мы изучали изменения легочной микроциркуляции в случае экспериментальной тромбоэмболии легочной артерии после применения β_1-блокатора небиволола, комбинированного блокатора α_1- и $\beta_{1,2}$-адренорецепторов карведилола и блокатора $\beta_{1,2}$-адренорецепторов пропранолола.

Результаты. После применения блокатора $\beta_{1,2}$-адренорецепторов — пропранолола и β_1-блокатора — небиволола большинство параметров легочной микроциркуляции возрастало. Комбинированный блокатор α_1- и $\beta_{1,2}$-адренорецепторов — карведилол оказывал вазодилататорные эффекты в основном на легочные артериальные сосуды, тогда как сопротивление венозных сосудов легких повышалось. Тромбоэмболия легочной артерии после применения бета-блокаторов приводила к выраженному возрастанию давления в легочной артерии, прекапиллярного и легочного сосудистого сопротивлений. В указанных условиях прирост коэффициента капиллярной фильтрации после применения карведилола был в два раза больше, чем после применения пропранолола. После введения небиволола коэффициент капиллярной фильтрации возрастал меньше, чем после применения пропранолола.

Заключение. Острая тромбоэмболия легочной артерии вызывала менее выраженное повышение коэффициента капиллярной фильтрации после применения небиволола по сравнению с карведилолом и пропранололом.

Ключевые слова: тромбоэмболия легочной артерии; легочная микрогемодинамика; коэффициент капиллярной фильтрации; небиволол; карведилол; пропранолол.

Introduction

Beta-blockers are widely used in modern clinical cardiology for the treatment of ischemic heart disease [1]. The novel generations of such drugs as combined α_1-, $\beta_{1,2}$-blocker carvedilol and selective β_1-blocker nebivolol, which can also stimulate β_3-adrenoceptors, had been shown to promote beneficial effects in such patients [2]. In the review article O. Kamp et al. noted, that nebivolol has beneficial effects on pulmonary artery pressure, pulmonary wedge pressure, exercise capacity and left ventricular ejection fraction [3]. There are literature data confirming the effectiveness of selective beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease [1]. H. Fujio et al. [4] showed that carvedilol could inhibit proliferation of cultured pulmonary artery smooth muscle cells of patients with idiopathic pulmonary arterial hypertension. In the experimental study E.A. Pankey et al. [5] established, that nebivolol treatment attenuated pulmonary hypertension, reduced right ventricular hypertrophy and improved pulmonary artery remodeling in monocrotaline-induced pulmonary hypertension in rats. The authors suggested, that nebivolol stimulates β_3-adrenoceptors and induces vasodilatation by increasing NO production [5]. However, it is unknown what will be the effects of these drugs on pulmonary microhemodynamics, in particular, capillary filtration coefficient. Especially, it should be stressed, that pulmonary thromboembolism can develop in patients with ischemic heart disease which are treated with beta-blockers. In comparative study A. Al-Ogaili et al. [6] showed, that the rate of venous thromboembolism occurrence in patients with ST-segment elevation myocardial infarction was 10 per 1000 admissions. However, there are no data concerning the pulmonary microcirculatory changes in cases of pulmonary embolism after pretreatment with nebivolol and carvedilol. For this reason, our research project was undertaken to compare pulmonary microcirculatory changes in case of experimental pulmonary thromboembolism in isolated rabbits' lungs after pretreatment with nebivolol, carvedilol and propranolol.

Materials and methods

The study was carried out according to ethical standards, approved of legal acts of the Russian Federation, principles of Basel declaration and recommendations of the Local Ethic Committee of the Institute of the Experimental Medicine (protocol 3/19 dated 25.04.2019).

The experiments were carried out on 35 male rabbits 3.0–4.0 kg body weight, which were anesthetized with warmed mixture of urethane and alpha-chloralose (Sigma Chemical Co., USA) 500 and 50 mg/kg, respectively, dissolved in 20 ml of saline solution, intraperitoneally), with sternotomy and mechanical ventilation, performed with "Faza-9" respirator (Russia). Rabbits were ventilated with tidal volume of 12–15 ml/kg and respiratory rate 30–40 breaths/min. The parameters of the mechanical ventilation were corrected to prevent hypoxic and acid-base balance disorders in animals. The blood gases values were controlled with ABL-50 blood-gas analyzer (Radiometer, Denmark).

After anesthesia rabbits were placed in a supine position and fixed on a heating table, and 1 ml of blood was taken from left jugular vein into syringe and catheter (15 cm long with an approximately 0.8 mm inner diameter). 10–15 cylindrical emboli (diameter 0.8 mm, length 1–1.5 mm) were made within 1 hr. after the removal of the blood clots from the syringe and catheter. This method of preparing blood clots was modified from the study of H.M. Chen et al. [7]. Then heparin (1000 U/kg) was injected into left jugular vein, left carotid artery was catheterized, and blood was removed from this artery into the heating reservoir, and as much blood as possible was collected. To fill completely the perfusion system 100–150 ml of dextran solution was added, and the total volume of perfusion system was nearly 300 ml. Sternum was removed, pericardium dissected, aorta, cranial and caudal veins were ligated to prevent retrograde blood flow. Pulmonary artery and left atrium were cannulated with plastic tubes diameter 4–5 mm, which were connected to the pump and then the lungs were perfused.

For estimation of capillary filtration coefficient (K_{fc}) in the lungs gravimetric methods are used by many investigators: R.O. Dull et al. [8], F. Ketabchi et al. [9], C.C. Bravo-Reyna et al. [10]. To perform K_{fc} calculation it is necessary to have a perfusion system that allows the acquisition of lung weight in real time, pulmonary arterial pressure, pulmonary venous pressure and capillary pressure, which is obtained by the double occlusion method from an isogravimetric state [10]. As authors stated, the lungs were not respired during the first 18–20 min of the weight transients. Following this time period, during which lung weight was measured, the lungs were again respired, and the lung weight was followed until the lungs attained a new isogravimetric state [10]. However, the cessation of lungs ventilation for 20 min can lead to pronounced changes of pulmonary microcirculation due to possible development of hypoxic pulmonary vasoconstriction. Especially, in case of acute pulmonary embolism determination of K_{fc} within 18–20 min does not reflect exact picture of the pulmonary microcirculatory changes. For all these reasons, in our study mean capillary hydrostatic pressure and capillary filtration coefficient were estimated with method of the extracorporeal circulating blood volumometry, which was proposed and described earlier by D.P. Dvoretsky [11]. We modified that approach to determine capillary hydrostatic pressure and K_{fc} in the whole lungs, using dual-chambers membranous piston pump of constant flow rate (136 ml/min), which was designed and manufactured in Institute of Experimental Medicine [12]. The schematic representation of lungs perfusion is presented on Figure.

The first pump (1st Pump chamber) forced the blood from the heating reservoir into the pulmonary artery (PA). From the left atrium, the blood flowed into the additional cylindrical glass extracorporeal reservoir (diameter 1.5 cm, length 25 cm), and the second pump (2nd Pump chamber) returned it into the heating reservoir. Therefore, in experiments the pulmonary artery (PA) pressure, left atrial (LA) pressure and extracorporeal reservoir (ECR) pressure were measured with MLT 0699 (AD Instruments, Australia) pressure transducers. The pre- and postcapillary resistance, pulmonary vascular resistance were calculated using Poiseuille's formula as: $R_a = (PAP - P_c)/PAF$; $R_v = (P_c - LAP)/PAF$; $PVR = (PAP - LAP)/PAF$, or, logically, $PVR = R_a + R_v$, where R_a — precapillary resistance, R_v — postcapillary resistance, PVR — pulmonary vascular resistance, PAP — pulmonary artery

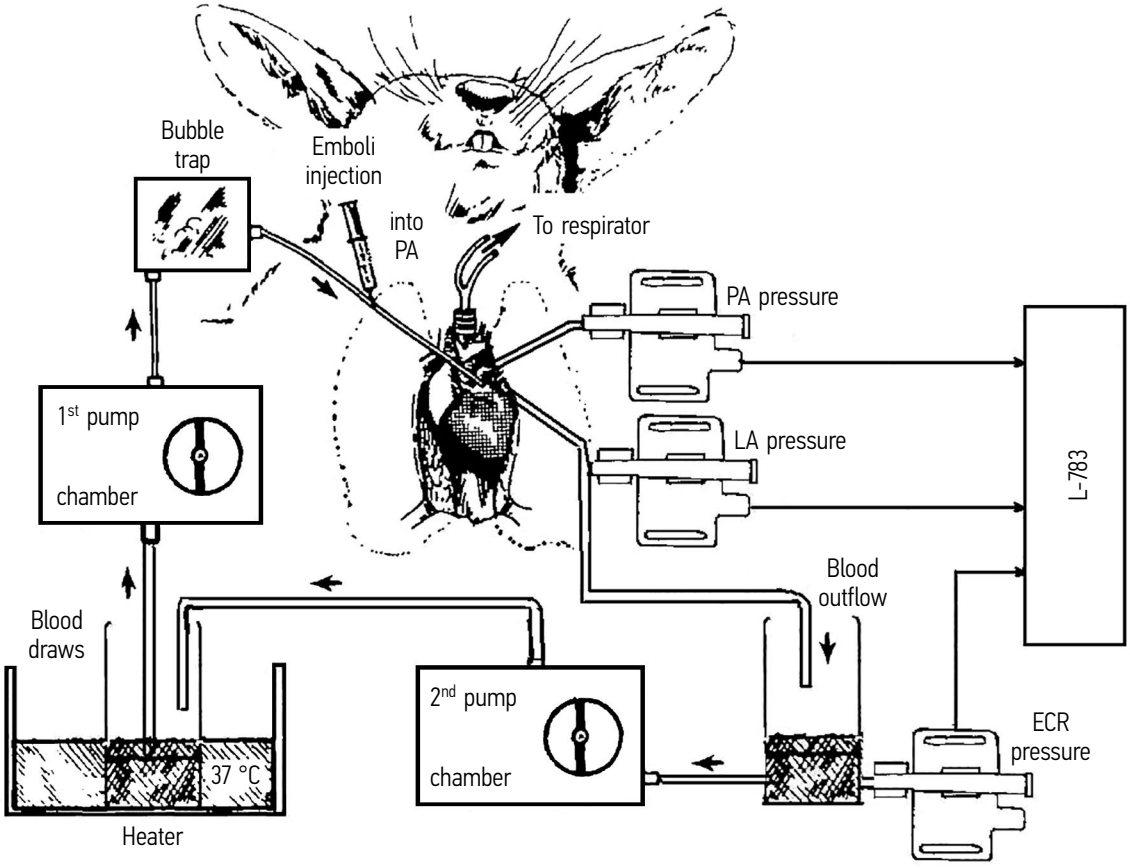

Figure. Schematic representation of methods of the isolated lungs perfusion with twin pump. PA — pulmonary artery; LA — left atrial; ECR — extracorporeal reservoir. Some parts of the figure were taken from the article: Catravas J.D. Removal of adenosine from the rabbit pulmonary circulation *in vivo* and *in vitro*. *Circ. Res.* 1984;54(5):603–611. DOI: 10.1161/01.res.54.5.603

perfusion pressure, P_c — mean capillary hydrostatic pressure, LAP — left atrial pressure, PAF — baseline value of the pulmonary artery flow (136 ml/min). Then pre-/postcapillary resistance ratio (R_a/R_v) was also calculated.

The baseline value of the pulmonary artery perfusion pressure was 23 ± 3 mm Hg, the left atrial pressure — 4.8 ± 0.3 mm Hg, i.e., approximately the same as in animals with intact circulation. The initial pressure in extracorporeal reservoir was 10 ± 2 mm Hg. The changes of the ECR pressure by 1 mm Hg reflected the changes of ECR blood volume by 2.38 ml, i.e. this method was very sensitive.

Folin–Ciocalteu method was used for determination of the total catecholamines concentration in the blood flowed from the lungs. Because this method is a convenient and simple, it widely applied for determination of the total phenolic contents in natural products [13]. The Folin–Ciocalteu reagent, trichloroacetic acid and sodium carbonate were purchased from LenReactive (Russia). To separate plasma 3 ml of the heparinized blood was centrifuged (centrifuge LMC-3000, Latvia) 1000 rpm for 10 min. To precipitate the proteins 0.1 ml plasma was added to 1 ml 5% solution of trichloroacetic acid, and samples were centrifuged again 2000 rpm for 20 min. The supernatants were collected. Then 4 ml 10% solution of sodium carbonate was added to samples and 0.5 ml of the Folin–Ciocalteu reagent was added. After 5 min the concentration of the catecholamines in the samples were measured at 650 nm with the photometer KFK-3-01 (Russia). Initially, the photometer was calibrated with standard 0.1% solution of adrenaline (Russia).

Five series of the experiments were carried out on perfused isolated lungs in situ. In the first series of experiments (7 rabbits, control) the acute pulmonary thromboembolism was modelled by injection from syringe of 10–15 autologous cylindrical emboli, suspended in 5 ml of saline solution, into the pulmonary artery through the T-shape triplex catheter, connected with the perfusion pump. In the next (2–5) series of experiments the acute pulmonary thromboembolism was modelled after pretreatment (as it was indicated above) with adrenoblockers dissolved in 5 ml of saline solution. The drugs were injected into pulmonary artery as it was described above.

In the second and third series of experiments (8 and 7 rabbits, respectively) we used propranolol (Obsidan, ISIS Pharma, Germany) (2–2.5 mg/kg) [14] and nebivolol (Nebilet, Berlin-Chemie AG, Germany) (0.1–0.2 mg/kg) [15], respectively. In the fourth and fifth series of experiments (6 and 7 rabbits, respectively) we used carvedilol (Carvedilol, Zentiva k.s., Chesh Republic) (0.2–0.5 mg/kg) [4] and non-selective alpha-blocker phentolamine (Russia) (2.5–5.0 mg/kg) [16]. The tablet forms of nebivolol, carvedilol and phentolamine were preliminarily dissolved in 10 ml of saline solution and then the drugs were diluted to necessary doses.

The measured pulmonary microcirculation parameters were digitized and sampled on hard drive of IBM PC Pentium, used L-Card L-783 analog-to-digital converter. The calculated parameters were estimated and analyzed with ACTest computer program (v.1.6.59, Laboratory of Automated Systems, Russia). The changes of investigated hemodynamic parameters were compared during 5 minutes after drugs and emboli injection, when pulmonary artery pressure changes were maximal. The statistical analysis was performed with Axum 5.0 (Math Soft Inc., USA) program. Student's *t*-test was used to verify the 0-hypothetis. The results were expressed in mean ± standard error of the mean; *P*-values less than 0.05 were considered as statistically significant. A Kolmogorov–Smirnov criterion was used for verification of experimental data for normal distribution.

Results

The base level values of pulmonary microcirculation parameters in rabbits of all series of experiments are summarized in Table 1.

The changes of pulmonary microcirculation parameters after propranolol and nebivolol administration were approximately the same (Table 1). Pulmonary artery pressure and capillary hydrostatic pressure increased; left atrial pressure did not change significantly. In both cases the calculated parameters of precapillary resistance (R_a), postcapillary (venous) resistance (R_v), pulmonary vascular resistance increased by 30–35% above baseline level, and for this reason pre/postcapillary resistance ratio (R_a/R_v) did not change. Capillary filtration coefficient in both cases increased to the same level, which could be explained by elevating of capillary hydrostatic pressure and postcapillary resistance (Table 1). Hence, after blockade of $\beta_{1,2}$-adrenoceptors by propranolol and β_1-adrenoceptors by nebivolol the most of the pulmonary microcirculatory parameters increased as a result of activation of $\alpha_{1,2}$-adrenoceptors of pulmonary arterial and venous vessels, caused by neurogenic sympathetic adrenergic influences.

After carvedilol administration pulmonary artery pressure, pulmonary vascular resistance and precapillary resistance decreased. However, capillary hydrostatic pressure and postcapillary resistance elevated and capillary filtration coefficient did not change. The relatively constant level of capillary filtration coefficient in case of elevating of capillary hydrostatic pressure and postcapillary (venous) resistance could be explained by decreasing of the pulmonary artery pressure and, especially, the precapillary resistance (Table 1). Therefore, carvedilol caused mainly vasodilatory effects of pulmonary arterial

Table 1

The changes of the pulmonary microcirculation parameters in the perfused rabbit's lungs with adrenoblockers pretreatment

Parameter	Baseline values for I–V series of experiments	The changes of parameters (%) vs. baseline values after blockade of adrenoceptors with:			
		propranolol *n* = 8	nebivolol *n* = 7	carvedilol *n* = 6	phentolamine *n* = 7
Pulmonary artery pressure	23 ± 3 mm Hg	30 ± 6**	27 ± 4**	–10 ± 3*	–21 ± 6*
Left atrial pressure	4.8 ± 0.3 mm Hg	6 ± 3	–5 ± 3	7 ± 3	–20 ± 4**
Pulmonary artery flow	136 ml/min	0	0	0	0
Capillary hydrostatic pressure (P_c)	7.5 ± 0.6 mm Hg	16 ± 4**	11 ± 3**	19 ± 4**	–7 ± 4
Pulmonary vascular resistance	178 ± 14 dyn×s×cm^{-5}	34 ± 7**	36 ± 8**	–16 ± 5*	–17 ± 6*
Precapillary resistance (R_a)	152 ± 22 dyn×s×cm^{-5}	34 ± 6**	36 ± 7**	–29 ± 6**	–24 ± 5**
Postcapillary resistance (R_v)	26 ± 4 dyn×s×cm^{-5}	30 ± 5**	35 ± 6**	38 ± 7**	8 ± 5
Pre/postcapillary resistance ratio (R_a/R_v)	5.8 ± 0.8	4 ± 3	0 ± 1	–48 ± 8**	–24 ± 6**
Capillary filtration coefficient (K_{fc})	0.04 ± 0.008 ml/min/100 gr/mm Hg	25 ± 7**	25 ± 6**	0 ± 2	0 ± 2

N o t e: The baseline values of parameters and their changes are expressed as mean ± standard error of mean. The digits with (–) symbol — the decreasing of parameter. *$p < 0.05$; **$p < 0.01$. The absence of asterisk — insignificant changes of parameter. *n* — number of animals.

vessels, meanwhile, the pulmonary venous resistance increased. We suggested, that carvedilol blocked mainly α_1-adrenoceptors of pulmonary arterial vessels. To test our hypothesis, concerning the possible role of α_2-adrenoceptors in the constrictor reactions of pulmonary veins, the additional experiments were carried out with non-selective $\alpha_{1,2}$-blocker phentolamine.

After phentolamine administration pulmonary artery pressure, pulmonary vascular resistance, precapillary resistance and left atrial pressure decreased. Although postcapillary resistance did not change significantly as a result of decreasing of left atrial pressure, it should be stressed, however, that after pretreatment with carvedilol postcapillary resistance increased. In case of blockade both of $\alpha_{1,2}$-adrenoceptors by phentolamine capillary hydrostatic pressure had tendency to decrease (statistically not significant), capillary filtration coefficient did not change, which could be explained by decreasing of precapillary resistance approximately to the same extent as in case of carvedilol administration (Table 1). Therefore, our suggestion concerning the role of activation of α_2-adrenoceptors in the constriction of pulmonary veins after pretreatment with carvedilol was proved in experiments with phentolamine administration.

The changes of the pulmonary microcirculation parameters in case of pulmonary embolism after pretreatment with adrenoblockers are summarized in Table 2. After beta-blockers administration the pulmonary thromboembolism characterized by "mosaic picture" of the microcirculatory changes with expressed elevating of the pulmonary artery pressure, precapillary and pulmonary vascular resistance.

Therefore, in those conditions, the constrictors neurogenic and humoral influences on the pulmonary arterial vessels prevailed (Table 2). The elevating catecholamines level was determined in performed experiments. Baseline catecholamines concentration was 342 ± 12 mkg/l. After pulmonary embolism it increased by 14 ± 3 % ($p < 0.05$) above baseline values.

For better analysis of the pulmonary microcirculatory changes, pairs of adrenoblockers were compared, when the changes of capillary hydrostatic pressure were approximately to the same extent, i.e. propranolol and carvedilol; nebivolol and phentolamine (Table 2). As noted above, in case of pulmonary thromboembolism after pretreatment with propranolol and carvedilol capillary hydrostatic pressure and precapillary resistance increased approximately to the same extent. However, postcapillary resistance after pretreatment with propranolol

Table 2

The changes of the pulmonary microcirculation parameters of perfused rabbit's lungs in case of pulmonary thromboembolism after pretreatment with adrenoblockers

Parameter	The changes (%) of parameters during pulmonary thromboembolism				
	In control animals *n* = 7	After blockade of adrenoceptors with:			
		propranolol *n* = 8	nebivolol *n* = 7	carvedilol *n* = 6	phentolamine *n* = 7
Pulmonary artery pressure	90 ± 10**	153 ± 12**	178 ± 16**	111 ± 25**	42 ± 14*
Left atrial pressure	–4 ± 2	4 ± 3	4 ± 3	15 ± 4**	6 ± 3
Pulmonary artery flow	0	0	0	0	0
Capillary hydrostatic pressure (P_c)	17 ± 4**	22 ± 5**	7 ± 2**	17 ± 5*	7 ± 3
Pulmonary vascular resistance	111 ± 18**	186 ± 15**	209 ± 15**	146 ± 23**	50 ± 17*
Precapillary resistance (R_a)	120 ± 22**	209 ± 61**	255 ± 27**	207 ± 28**	62 ± 18**
Postcapillary resistance (R_v)	53 ± 6**	51 ± 16*	2 ± 2	15 ± 4**	13 ± 4*
Pre/postcapillary resistance ratio (R_a/R_v)	43 ± 7**	103 ± 14**	247 ± 28**	164 ± 18**	44 ± 10**
Capillary filtration coefficient (K_{fc})	25 ± 4**	60 ± 14**	20 ± 6*	125 ± 23**	50 ± 12**

N o t e: The changes of parameters to baseline values (in control animals) or to the level after pretreatment with adrenoblockers are expressed as mean ± standard error of mean. The digits with (–) symbol — the decreasing of parameter. *$p < 0.05$; **$p < 0.01$. The absence of asterisk — insignificant changes of parameter. *n* — number of animals.

increased more, than after carvedilol administration, which could be explained by adrenergic activation of both $\alpha_{1,2}$-adrenoceptors of pulmonary veins. After pretreatment with carvedilol postcapillary resistance increased three times less, than in control animals. That could be the result of that carvedilol caused the elevating of pulmonary venous resistance and thus it decreased the reserve of their constrictor reactions in case of pulmonary thromboembolism.

Especially, it should be stressed, that after pulmonary thromboembolism followed carvedilol administration capillary filtration coefficient was increased two times more than after pretreatment with propranolol (Table 2). The excessive elevating of this parameter could be result not only of the increasing of the precapillary resistance and the pre/postcapillary resistance ratio, but it could be caused also by the elevating of the permeability of endothelium of pulmonary vessels. It was noted, that in case of pulmonary thromboembolism after blockade of $\alpha_{1,2}$-adrenoceptors with phentolamine capillary filtration coefficient was increased less, than after blockade of α_1- and $\beta_{1,2}$-adrenoceptors with carvedilol (Table 2). Therefore, we suggested, that the catecholamines stimulation of the endothelial α_2-adrenoceptors in the conditions of the blockade of $\beta_{1,2}$-adrenoceptors could promote the increasing of the permeability of pulmonary vessels.

Pulmonary thromboembolism after pretreatment with nebivolol caused more elevating of precapillary resistance, than after phentolamine administration, but postcapillary resistance increased less, than in the last case. For this reason, in case of pulmonary embolism after pretreatment with nebivolol capillary filtration coefficient increased less, than after phentolamine administration. However, after pretreatment with nebivolol the elevating of capillary filtration coefficient had no statistically significant difference from that one in control animals, although in the last case the postcapillary resistance increased more expressively (Table 2). Hence, we suggested, that β_3-adrenoceptors activation by nebivolol could increase the endothelial permeability. In case of pulmonary thromboembolism after the blockade of $\alpha_{1,2}$-adrenoceptors by phentolamine, capillary filtration coefficient increased approximately 2 times more, than in control animals (Table 2). As pre/postcapillary resistance ratio (Ra/Rv) were practically the same in both cases, we suggested, that the increasing of capillary filtration coefficient was the consequence of mainly elevating of the permeability of the pulmonary vessels. Possibly, the increasing of permeability of the pulmonary vessels could be the result of catecholamines activation of the endothelium β_3-adrenoceptors, which was increased after the blockade of $\alpha_{1,2}$-adrenoceptors.

Discussion

Acute pulmonary embolism is characterized by activation of the sympathetic nervous system and enhanced catecholamines level. The elevated catecholamines concentration can hyperactivate platelets and accelerate their turnover [17]. In the experimental study of Y. Wang et al. it was shown, that upregulation of the sympathetic medium transmitters tyrosine hydroxylase and neuropeptide Y in whole lung tissues serves one of the pathological features of massive pulmonary embolism model associated with shock in rabbits [18]. In our study the blood plasma catecholamines level was also increased after modelling of acute pulmonary embolism in isolated perfused rabbits' lungs.

The current physiological literature data indicated, that activation of $\alpha_{1,2}$-adrenoceptors of both pulmonary arterial and venous vessels smooth muscles cells evokes vasoconstriction [19]. Meanwhile, the activation of $\beta_{1,2}$-adrenoceptors causes vasodilatation [20]. In our study after the blockade of $\beta_{1,2}$-adrenoceptors by propranolol and β_1-adrenoceptors by nebivolol the most of the pulmonary microcirculatory parameters increased as a result of activation of $\alpha_{1,2}$-adrenoceptors of pulmonary arterial and venous vessels, caused by neurogenic sympathetic adrenergic influences. Combined α_1-, $\beta_{1,2}$-blocker carvedilol caused mainly vasodilatory effects of pulmonary arterial vessels, but pulmonary venous resistance increased due to activation of α_2-adrenoceptors of pulmonary veins.

In our study for the first time the comparative analysis of the pulmonary microcirculatory changes in case of experimental acute pulmonary thromboembolism after adrenoblockers administration was performed. The current study showed, that pulmonary thromboembolism after pretreatment with propranolol, nebivolol and carvedilol caused more elevating of pulmonary artery pressure, precapillary and pulmonary vascular resistance than in control animals. Therefore, the constrictors neurogenic and humoral influences on the pulmonary arterial vessels prevailed. However, the significant differences were expressed in the changes of the capillary hydrostatic pressure, postcapillary resistance and capillary filtration coefficient (K_{fc}). The K_{fc} is defined as the product of the hydraulic conductivity and filtration surface area, and essentially measures the endothelial barrier permeability to convective water transport [21].

In case of pulmonary thromboembolism after pretreatment with carvedilol capillary filtration coefficient was increased two times more than after propranolol administration. The excessive elevating of this parameter could be the result not only of the increasing of the precapillary resistance, the pre/postcapillary resistance ratio, but also the increasing of the permeability of the endothelium of the pulmonary vessels. The different subtypes of α- and β-adrenoceptors are localized on the endothelial cells, where their activation can influence on the contractility of smooth muscles cells of the pulmonary vessels, and regulate the endothelial permeability through the release of nitric oxide [22]. In our experiments with modelling of the acute pulmonary thromboembolism the endothelial permeability could be increased after the blockade with carvedilol of α_1- and $\beta_{1,2}$-adrenoceptors and the catecholamines activation of endothelial α_2-adrenoceptors.

There are controversial literature data concerning the possible role of these adrenoceptors' subtypes in the regulation of the smooth muscles cell contractility and endothelial permeability. A.M. Pimentel et al. demonstrated the involvement of endothelial α_2-adrenoceptors in the clonidine-induced vasodilatation of the rat isolated mesenteric arterial bed due to increasing of nitric oxide release [23]. Later, F. Jantschak and H.H. Pertz showed, that α_2-adrenoceptors agonist UK14304 elicited only a slight contraction in pulmonary arteries compared to veins. Endothelium denudation failed to affect the UK14304 response. Authors concluded that postjunctional α_{2C}-adrenoceptors predominantly mediate contraction in porcine pulmonary arteries and α_{2C}-adrenoceptors antagonists may be beneficial in the treatment of pulmonary edema [24]. However, Q. Chen et al. demonstrated, that dexmedetomidine, α_2-adrenoreceptor agonist, was able to ameliorate remote pulmonary microvascular hyper-permeability induced by renal ischemia-reperfusion [25].

In our study in case of pulmonary thromboembolism after blockade of $\alpha_{1,2}$-adrenoceptors with phentolamine the capillary filtration coefficient was increased less, than after blockade of α_1- and $\beta_{1,2}$-adrenoceptors with carvedilol, in spite that in both cases postcapillary resistance increased approximately to the same extent. Therefore, we suggested, that in case of acute pulmonary embolism after pretreatment with carvedilol catecholamines stimulation of the endothelial α_2-adrenoceptors could promote the increasing of the permeability of pulmonary microvessels. However, in case of acute pulmonary embolism after pretreatment with carvedilol the pulmonary precapillary resistance increased more, than after phentolamine pretreatment, which could also be reason of the excessive increasing of capillary filtration coefficient.

In the case of acute pulmonary thromboembolism after pretreatment with nebivolol capillary hydrostatic pressure and capillary filtration coefficient increased to a lesser extent, than after propranolol administration and postcapillary resistance practically did not change. It could be caused by nebivolol activation of the endothelial β_3-adrenoceptors of the pulmonary venous vessels and increased nitric oxide synthesis [26]. M. Bäck et al. showed that

after leukotriene C4 and noradrenaline applications the constrictor reactions of the pulmonary veins are less expressed, compared with the pulmonary arteries, due to greater production of nitric oxide [27]. However, in case of pulmonary thromboembolism after pretreatment with nebivolol the increase of capillary filtration coefficient had no statistically significant difference from that one in control animals although in the last case the postcapillary resistance was elevated. For this reason, we suggested, that β_3-adrenoceptors activation could increase the endothelial permeability. In the review article W.N. Durán et al. stated, that the intensification of the nitric oxide production by endothelium promotes increasing of its permeability [28]. In our study in case of acute pulmonary thromboembolism after blockade of $\alpha_{1,2}$-adrenoceptors by phentolamine, capillary filtration coefficient was increased approximately two times more, than in control animals. As pre/postcapillary resistance ratio (R_a/R_v) were practically the same in both cases, we suggested, that the increasing of the capillary filtration coefficient was the consequence of mainly elevating of permeability of the pulmonary vessels. The last one could be the result of catecholamines activation of the endothelium β_3-adrenoceptors, which was increased after the blockade of $\alpha_{1,2}$-adrenoceptors. V. Spindler and J. Waschke demonstrated that inhibition of β-adrenergic receptors by propranolol increased hydraulic conductivity of rat postcapillary venules [29]. J. Yang et al. showed that the activation of β_2-adrenoceptors was able to protect the lung microvascular endothelial cells permeability from lipopolysaccharide injury [30]. However, as noted above, activation of the endothelial β_3-adrenoceptors of pulmonary vessels can increase nitric oxide synthesis and endothelial permeability [26].

Conclusions

1) After blockade of $\beta_{1,2}$-adrenoceptors by propranolol and β_1-adrenoceptors by nebivolol the most of the pulmonary microcirculatory parameters increased as a result of activation of $\alpha_{1,2}$-adrenoceptors of pulmonary arterial and venous vessels, caused by neurogenic sympathetic adrenergic influences.
2) Combined α_1-, $\beta_{1,2}$-blocker carvedilol caused mainly vasodilatory effects of the pulmonary arterial vessels, however, the pulmonary venous resistance increased due to activation of α_2-adrenoceptors of the pulmonary veins.
3) Pulmonary thromboembolism after pretreatment with beta-blockers caused pronounced increase of the pulmonary artery pressure, precapillary and pulmonary vascular resistance.
4) In case of pulmonary thromboembolism after pretreatment with carvedilol capillary filtration coefficient was increased two times more than after propranolol administration; after pretreatment with nebivolol capillary filtration coefficient increased less, than after carvedilol and propranolol administration.

Additional information

Funding. The study was performed according to state plan FGWG-2022-0006 and supported by Ministry of Education and Science of the Russian Federation.

Ethical approval. The study was approved of the Local Ethic Committee of the Institute of the Experimental Medicine (protocol 3/19 dated 25.04.2019).

Conflict of interest. No potential conflict of interest was reported by the authors.

Author contributions. All authors made a significant contribution to the study and the article preparation, as well as read and approved the final version before its publication. The largest contribution is distributed as follows: *V.I. Evlakhov* — conceptualization, methodology, data processing, project administration, writing and editing — original draft; *I.Z. Poyassov* — methodology, data processing, validation, editing — original draft; *T.P. Berezina* — methodology, data processing.

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Information about the authors / Информация об авторах

Vadim I. Evlakhov — MD, Dr. Sci. (Med.), Head of the Laboratory of the Physiology of Visceral Systems named after acad. K.M. Bykov. Institute of the Experimental Medicine, Saint Petersburg, Russia; Assistant Professor of the Department of Normal Physiology. Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia. ORCID: https://orcid.org/0000-0002-2521-8140; Scopus Author ID: 6603378175; eLibrary SPIN: 9072-4077; e-mail: viespbru@mail.ru

Ilya Z. Poyassov — Dr. Sci. (Biol.), Senior Research Fellow of the Laboratory of the Physiology of Visceral Systems named after acad. K.M. Bykov. Institute of the Experimental Medicine, Saint Petersburg, Russia; Professor of the Department of the Medical Electronics. Saint Petersburg State University of Aerospace Instrumentation, Saint Petersburg, Russia. ORCID: https://orcid.org/0000-0002-1700-7837; eLibrary SPIN: 7285-0493; e-mail: ilpoar@yandex.ru

Tatiana P. Berezina — Cand. Sci. (Biol.), Research Fellow of the Laboratory of the Physiology of Visceral Systems named after acad. K.M. Bykov. Institute of the Experimental Medicine, Saint Petersburg, Russia. ORCID: https://orcid.org/0000-0003-0647-2458; eLibrary SPIN: 6086-1663; e-mail: retaber@mail.ru

Вадим Иванович Евлахов — д-р мед. наук, заведующий лабораторией физиологии висцеральных систем им. К.М. Быкова. ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия; доцент кафедры нормальной физиологии. ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова», Санкт-Петербург, Россия. ORCID: https://orcid.org/0000-0002-2521-8140; Scopus Author ID: 6603378175; eLibrary SPIN: 9072-4077; e-mail: viespbru@mail.ru

Илья Залманович Поясов — д-р биол. наук, ведущий научный сотрудник лаборатории физиологии висцеральных систем им. К.М. Быкова. ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия; профессор кафедры медицинской радиоэлектроники. ФГАОУ ВО «Санкт-Петербургский государственный университет аэрокосмического приборостроения», Санкт-Петербург, Россия. ORCID: https://orcid.org/0000-0002-1700-7837; eLibrary SPIN: 7285-0493; e-mail: ilpoar@yandex.ru

Татьяна Павловна Березина — канд. биол. наук, научный сотрудник лаборатории физиологии висцеральных систем им. К.М. Быкова. ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия. ORCID: https://orcid.org/0000-0003-0647-2458; eLibrary SPIN: 6086-1663; e-mail: retaber@mail.ru

✉ Corresponding author / Контактное лицо

Vadim I. Evlakhov / Вадим Иванович Евлахов
Адрес: Россия, 197022, Санкт-Петербург, ул. Академика Павлова, д. 12
Address: 12 Academician Pavlov St., Saint Petersburg, 197022, Russia
E-mail: viespbru@mail.ru