ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.12-008.331.1:615

Effect of oxacom on the right ventricular pressure in rats with monocrotalin-induced pulmonary arterial hypertension

A. A. Abramov, V. L. Lakomkin, A. A. Timoshin, E. V. Lukoshkova, V. V. Ermishkin, V. I. Kapelko
National Medical Research Centre in Cardiology, Moscow, Russia

Corresponding author:
Aleksandr A. Abramov, Laboratory of Experimental Heart Pathology, Institute of Experimental Cardiology, National Medical Research Centre in Cardiology, 15 a 3 Cherepkovskaya street, Moscow, 121552 Russia.
Phone: +7(495)414–67–55.
Fax: +7(495)414–66–99.
E-mail: ferk_88@list.ru

Received 24 May 2017;
accepted 2 October 2017.

Abstract

Background. Pulmonary arterial hypertension (PAH) is a relatively rare disease, but its therapy is expensive and effectiveness is moderate. One of important mechanisms of PAH pathogenesis is reduced formation of nitric oxide in pulmonary vascular endotheliocytes. **Objective.** To study the effect of oxacom (dinitrosyle iron complex with ligand glutathione), which already demonstrated long-term decline in blood pressure (BP) in systemic circulation, on pressure in pulmonary circulation. **Design and method.** To induce PAH, the standard monocrotalin rat model was used. Three weeks after monocrotalin introduction (60 mg/kg), a catheterization of the right ventricle was performed in anesthetized rats (100 mg/kg ketamine) through jugular vein and pressure was measured. Simultaneously, BP in femoral artery and ECG were recorded. **Results.** Systolic pressure in the right ventricle (SPRV) in rats after monocrotalin introduction doubled compared with the control group, from 35 to 70 mmHg, but myocardial contractility index fell by 28 %, also duration of QRS complex and the height of T-wave increased. Intravenous oxacom (40 mg/kg) quickly reduced SPRV by average of 12 ± 3 mmHg, and this level was maintained for an hour. This effect was absent in control rats. Similar BP changes in systemic circulation were observed in both groups. Inhalation of nitric oxide led to BP decrease only in animals with high level of SPRV. Inhalation of oxacom was ineffective. **Conclusion.** Oxacom is a promising substance for sustained pressure decline in the pulmonary circulation in PAH, but further investigations are needed for the development of a more suitable prolonged-action form of the drug.

Key words: pulmonary arterial hypertension, nitric oxide, monocrotalin, dinitrosyle iron complexes, blood pressure

For citation: Abramov AA, Lakomkin VL, Timoshin AA, Lukoshkova EV, Ermishkin VV, Kapelko VI. Effect of oxacom on the right ventricular pressure in rats with monocrotalin-induced pulmonary arterial hypertension. Arterial'naya Gipertenziya = Arterial Hypertension. 2017;23(5):412–420. ***doi:10.18705/1607-419X-2017-23-5-412-420***

Действие оксакома на давление в правом желудочке у крыс с легочной артериальной гипертензией, индуцированной монокроталином

А. А. Абрамов, В. Л. Лакомкин, А. А. Тимошин, Е. В. Лукошкова, В. В. Ермишкин, В. И. Капелько
Федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр кардиологии» Министерства здравоохранения Российской Федерации, Москва, Россия

Контактная информация:
Абрамов Александр Александрович,
ФГБУ «НМИЦ кардиологии» Минздрава России,
3-я Черепковская ул., д. 15 а, Москва, Россия, 121552.
Тел.: +7(495)414–67–55.
Факс: +7(495)414–66–99.
E-mail: ferk_88@list.ru

Статья поступила в редакцию 24.05.17 и принята к печати 02.10.17.

Резюме

Легочная артериальная гипертензия (ЛАГ) — относительно редкое заболевание, но терапия его дорога и малоэффективна. Одним из важных механизмов патогенеза ЛАГ является сниженное образование оксида азота в эндотелиоцитах легочных сосудов. **Цель исследования** состояла в изучении эффекта оксакома (динитрозильный комплекс железа с лигандом глутатионом), уже зарекомендовавшего себя как средство длительного снижения артериального давления (АД) в большом круге кровообращения, на давление в малом круге. **Материалы и методы.** Для воспроизведения ЛАГ была использована стандартная монокроталиновая модель на крысах. Через 3 недели после введения монокроталина (60 мг/кг) у наркотизированных крыс (кетамин 100 мг/кг) катетеризировали правый желудочек через яремную вену и измеряли давление в нем. Одновременно регистрировали АД в бедренной артерии и электрокардиограмму. **Результаты.** Систолическое давление в правом желудочке (СДПЖ) у крыс, получивших монокроталин, возросло вдвое по сравнению с контрольной группой — с 35 до 70 мм рт. ст., но индекс сократимости миокарда снизился на 28%, увеличилась длительность комплекса QRS, возрос зубец Т. Внутривенное введение оксакома (40 мг/кг) этим животным быстро снижало СДПЖ в среднем на 12 ± 3 мм рт. ст., и этот уровень сохранялся на протяжении часа наблюдения. У контрольных крыс такой эффект отсутствовал. АД в большом круге в обеих группах изменялось одинаково. При ингаляции оксида азота гипотензивное действие наблюдали только у животных с повышенным уровнем СДПЖ. Ингаляционное введение оксакома оказалось неэффективным. **Заключение.** Результаты показали, что оксаком является перспективным средством для устойчивого снижения давления в малом круге кровообращения при ЛАГ, но требуется дальнейшая работа по созданию модифицированной формы газообразного оксакома, способного проникать через легочные альвеолы.

Ключевые слова: легочная артериальная гипертензия, оксид азота, монокроталин, динитрозильные комплексы железа, артериальное давление

Для цитирования: Абрамов А. А., Лакомкин В. Л., Тимошин А. А., Лукошкова Е. В., Ермишкин В. В., Капелько В. И. Действие оксакома на давление в правом желудочке у крыс с легочной артериальной гипертензией, индуцированной монокроталином. Артериальная гипертензия. 2017;23(5):412–420. ***doi:10.18705/1607-419X-2017-23-5-412-420***

Introduction

Pulmonary arterial hypertension (PAH) is a relatively rare disease but it is very difficult to curable. Currently, PAH is defined as a chronic increase in-blood pressure in the pulmonary artery (greater than 25 mmHg at rest and over 30 mmHg during physical exercise, when pressure jamming is <15 мм [1]. WHO classified the PAH in the first group of diseases [2].

The etiology of this disease is diverse. The main causes of PAHare hypoxia, inflammation or genetic defects. But the pathogenetic changes may be similar. At long noncompensatedPAHthe vascular wall remodeling in the small circle of blood circulation develops, disrupted normal gas exchange, and increased load on the right ventricle leading to myocardial hypertrophy, and then to right side failure, the so-called "cor pulmonale" [3]. In chronic PAH, characteristic anatomical changes in the vascular wall are mostly of inflammatory nature: obliteration vascular bed, overgrowth of connective tissue, the substitution of functional elements of the vascular wall by fibroblasts [4,5]. Remodeling occurs in all segments of the vascular wall, it involved both endothelial and smooth muscle cells [6].

A better study of the pathogenesis may be done atan adequate experimental model. However, currently there is no preclinical model that would fully play the character of PAH in humans [7,8]. Nevertheless, a study of models allows to identify cellular changes that are useful for understanding the pathogenesis of this disease. The inflammatory process in endotheliocytes is one of the main reasons in the pathogenesis of PAH, it causes an increase in the permeability of the endothelial layer, reducing the NO-synthase activity [9] and the growing influence of endothelin, thromboxane and other vasoconstricting molecules. The result is a steady increase in vascular tone in this field of the system.

As a PAH model of an inflammatory nature, alkaloid monocrotalin is widely used. It causes damage to the pulmonary endothelium, as well as coronary arteries and combined with damage to alveoli. Pulmonary endothelium is damaged more just because itis the first to stand in the way of substances introduced intravenously and has a large surface area, all cardiac output of blood goes through the lung capillaries. As a result of increased permeability of the endothelial layer, a swelling of lung tissue and blood vesselsdevelops, worsening the diffusion of oxygen and carbon dioxide. In addition, under the influence of hypoxia a disrupted superoxide formation in myocyte mitochondria occurred, accompanied by a shift of the potential up facilitating Ca^{++} penetration followed by stable increase tonus of arteries.

It is obvious that the PAH therapy should be aimed primarily at overcoming endothelial dysfunction. Therefore, attempts to restore the level of nitric oxide are pathogenetically justified. The most promising and pathogenetically justified is the treatment by nitric oxide because it has an effect similar to the endothelium-relaxing factor. Nitric oxide production is an important antitromboticfactor. Inhalation of nitric oxide is already applied in the clinic, but its effect is limited to short time of inhalation. NO free content and its derivatives is reduced in whole blood, but increases in the tissues of the heart and lungs [10]. The authors interpret these changes as weakening function of eNOS and increased inflammation. At the same time they record the presence of signs of oxidative stress (increase of TBA-reactive products and reduced glutathione in the lungs), and suggest that this makes an additional contribution to the reduction of free NO level and its derivatives in blood.

In this paper we have attempted to achieve a more prolonged hypotension in the small circle using a novel nitric oxide donor and ways of introduction. During the last decade in our cardiocentera preparation containing dinitrosyle iron complexes (DNIC) with the ligand glutathione was created with the help of prof. A. F. Vanin [11]. This compound is a natural depot of nitric oxide in cells, it increases DNIC associated with proteins and its content in organs at different types of introduction accompanied by prolonged hypotensive effect. The drug was given the name "Oxacom", after preclinical investigation it has been applied to healthy volunteers and patients with hypertonic crisis [12]. In this regard, the purpose of this work was to study oxacom effect, as well as nitric oxide, in PAH induced by monocrotalin.

Materials and methods

Experiments were performed on ketamine-anesthetized (100 mg/kg) male Wistar rats weighing 400–450 g. All manipulations with laboratory animals were done in compliance with the requirements of the Animal Use and Care Committee of the Russian Cardiology Research and Production Complex and the principles of Good Laboratory Practice (national standard of the Russian Federation GOST

P 53434–2009). Monocrotalin alkaloid was injected intravenously at a dose of 60 mg/kg. Through 3–4 week after monocrotalin introduction the ECG was registered in acute experiments on anesthetized rats (100 mg/kg ketamine). The right ventricle (RV) was catheterizedthrough the jugular vein with polyethylene PE-50 catheter (Instech Salomon) andRV pressure was recordedwith tensometric amplifier Hugo Sachs Elektronik (Germany). The catheterend was made curved in accordance with the recommendations [13]. The average blood pressure (BP)was recorded with tensometric amplifierGould Statham P23 Db (USA).

ECG and pressure signals were recorded using "Biograph-4" system (Saint-Petersburg State University of Aerospace Instrumentation, Russia) and directed at frequency of 1 kHz through the analog-to-digital converter NI USB-6210 (National Instruments, USA) to computer hard disk. Original programs (written by E. V.L.) were designed for recording and processing of physiological signals. Parameter calculation was performed based on the analysis of primary recorded signals with their preliminary pulse-synchronous averaging for 40 cardiocycles every 5 sec. For this purpose, as the first step, interpolation and digitization of ECG signal segments containing QRS complex were performed using 0.2 ms steps that is needed for accurate determination of the position of the R peak in each cardiocycle. Next, all fragments of the pulse wave signals were synchronized with the R peak and median filtering was performed to remove noise and waves that may be different in shape or amplitude.Traditional indices of ventricular contractility, namely maximum rate of pressure development (+dP/dt max) and the contractility index (dP/dt max/P), normalized to pressure at the peak of +dP/dt maximum, were determined.

Oxacom (40 mg/kg) was injected intravenously as a bolus. In addition, an inhaled route of oxacom and nitric oxide (0.1 % medical mix) administration was used. A tube for gaseous substance was fixed on the nose of the animal. Fixation was not tight to prevent hypoxia and asphyxia and thus all inhaled substanceswere supplied overdosed. Nitric oxide was supplied with a rate 200 ml/min for half an hour. Oxacominhalation was performed in the same animal after half an hour after the end of NO introduction. Oxacombefore introduction was dissolved in saline solution up to a concentration of 10 mg/mlandinhaledwithin an hour using ultrasonic nebulizer Omron Micro Air NE-U22. During this time 20 ml of the solution was spent.

Statistical processing of experimental data was performed using Statistics Package in Microsoft Excel 2013 and Student's t-test. Experimental values from in vivo experiments are presented as M±SEM. Statistically significant differencewas considered atp<0.05.

Results

The original parameters of RV function are shown in Fig. 1 and Table 1. In rats injected with monocrotalin the RV systolic blood pressure was twice higher as compared to control animalsthat reflects elevated pressure in the pulmonary artery. Accordingly, both maximal rates of pressure de-

Fig. 1.Typical examples of ECG, right ventricular pressure (RVP) and RVP first derivative during cardiocycle in both groups of animals

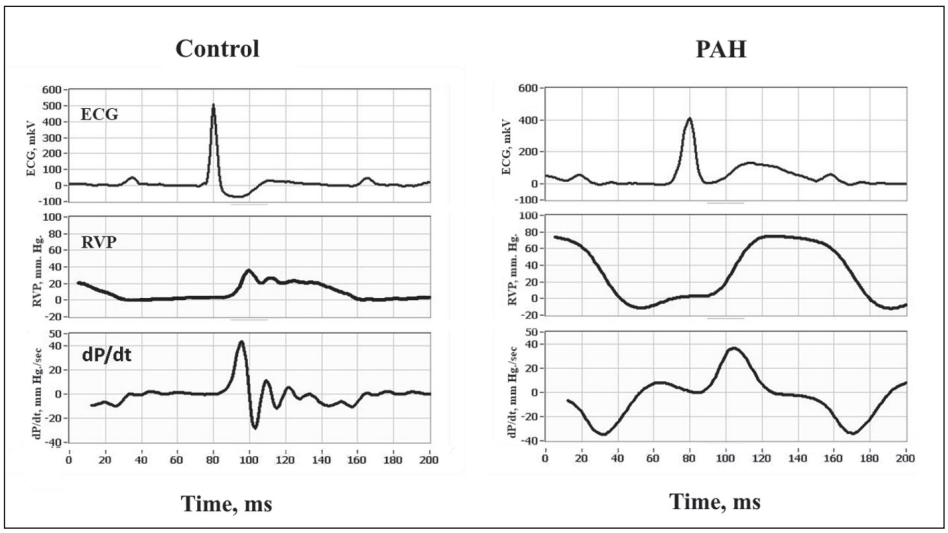


Table 1

INITIAL PARAMETERS OF THE RIGHT VENTRICULAR FUNCTION 3 WEEKS AFTER MONOCROTALIN

	Control	Monocrotalin
Number of rats	9	9
Heart rate, min-1	410 ± 7	409 ± 9
Arterial pressure, mmHg	136 ±3	134 ± 5
RV systolic pressure, mmHg	35 ± 2	70 ± 5 **
RV diastolic pressure, mmHg	0,5 ± 1,0	2,7 ± 1,0
+dP/dt max, mmHg/s	3500 ± 294	4770 ± 761 *
Contractility index (s-1)	171 ± 8	124 ± 10 **

Note: * — $p < 0,05$; ** — $p < 0,01$.

velopment and fall were increased. However, the myocardial contractility index was lower by 28%. Also, in these animals the duration of QRS complex was longer and T prong, not very pronounced in the control group, increases in amplitude and duration in monocrotalin-injectedrats, becoming prominent.The arterial pressure in the higher circle and heart rate were similar in both groups.

Intravenous Oxacom administration intomonocrotalin-injected rats had a strong hypotensive action in small circle, RV systolic pressure decreased after 2 min to 58±3 mmHg and remained at this level during an hour (fig. 2). The average AP in the big circle also steadily declined from 134±5 to 111±5 mmHg.The hypotensive action in control animals was similar, but in the small circle only short hypotensive effect, by 2–5 min, was observed. In both groups the drug poorly affect the RV diastolic pressure. The RV contractility index increased significantly by 9% ($p < 0.05$), whereas in the control group it was not changed. Thus, the main Oxacomeffect was the steady decline of high pressure in the small circle.

Inhaled NO introduction to monocrotalin-injected rats decreased RV systolic pressure but not in all experiments, this effect was observed in 6 rats while 3 animals were ineffective (fig. 3). The data in figure 3 shows that NO-induced hypotensive action was observed only in rats with elevated RV systolic pressure and not observed in those animals in which it was onlymoderately raised. Effect of nitric oxide had developed rapidly, almost immediately after the start of inhalation, and ceased promptly after the cessation of the inhalation.Subsequent inhalation with Oxacomfailed to reduce the RV pressure in any group of animals.

Discussion

Our data showed that in 3 weeks after monocrotalin injection the RV systolic pressure increased from 35 to 70 mmHg, which is consistent with literature data [14,15]. It should be noted that the procedure of RV catheterization is harder than for LV, and due to this in works of some authors the animal death rate reached to 80% of rats and instead some branches of the pulmonary artery were catheterizedat with opened chest [16]. They found an increased pressure in the pulmonary artery from 12±5 up to 22±7 mm Hg through 3 weeks after the monocrotalinintroduction, i. g. roughly the same twice rise, as RV pressure increase in our experiments. This increase was noticed after 1–2 week [17,18], and makes the reason for significant RV hypertrophy, emerging after 12 days [19]. Myocardial hypertrophy predisposes to changes of its electrical properties — action potential and QRST complex elongated [20], a potential dispersion increased, and susceptibility to arrhythmogenesisoccurred [21]. However, in vivo RV function can be successfully compensated [22], and only a violation of the RV diastolic pressure is the earliest diagnostic criterion [23].

Relatively later occurrence of pulmonary hypertension is due to the gradual development of the destructive processes in lung endothelium. After 3–4 day a significant activation of DNA pulmonary endotheliocytesoccurs [18]. A reactive monocrotalinmetabolite, dehydromonocrotalin, produced in the liver, is the acting toxic substance, it damages not only endotheliocytes, but also lung alveoli. As a result, their permeabilityincreases, resulting in developing ofpulmonary edema [24].The consistent study of lung function during 1–3 weeks after the monocrotalin introduction showed that most early symptoms

Fig. 2. Effect of intravenous oxacom injection on mean arterial pressure in the large circle (upper curves) and RV systolic pressure (lower curves) in the control and monocrotalin-injected groups

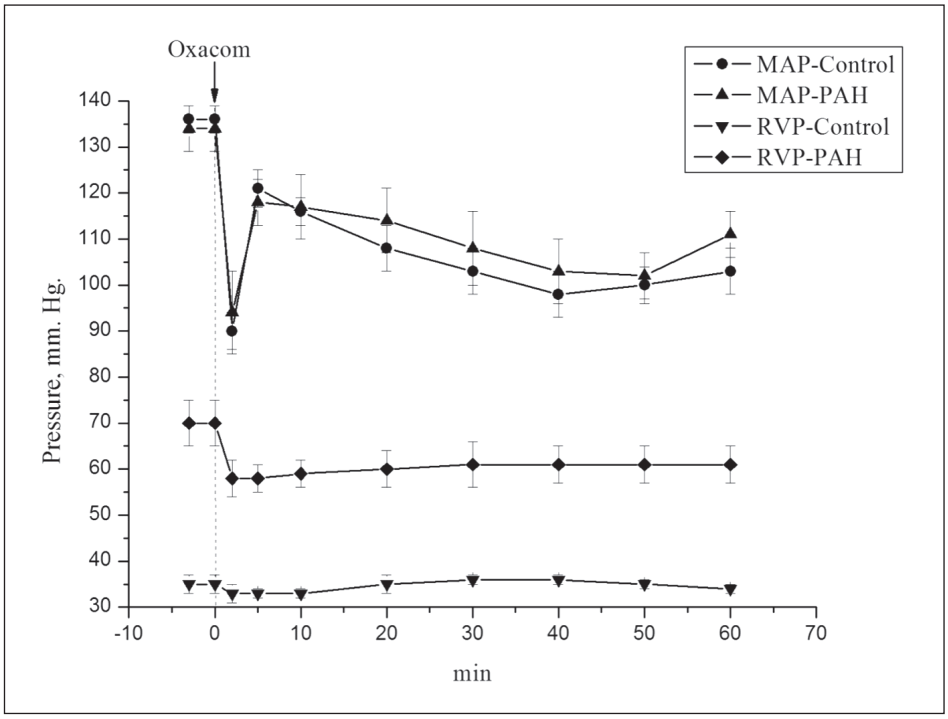
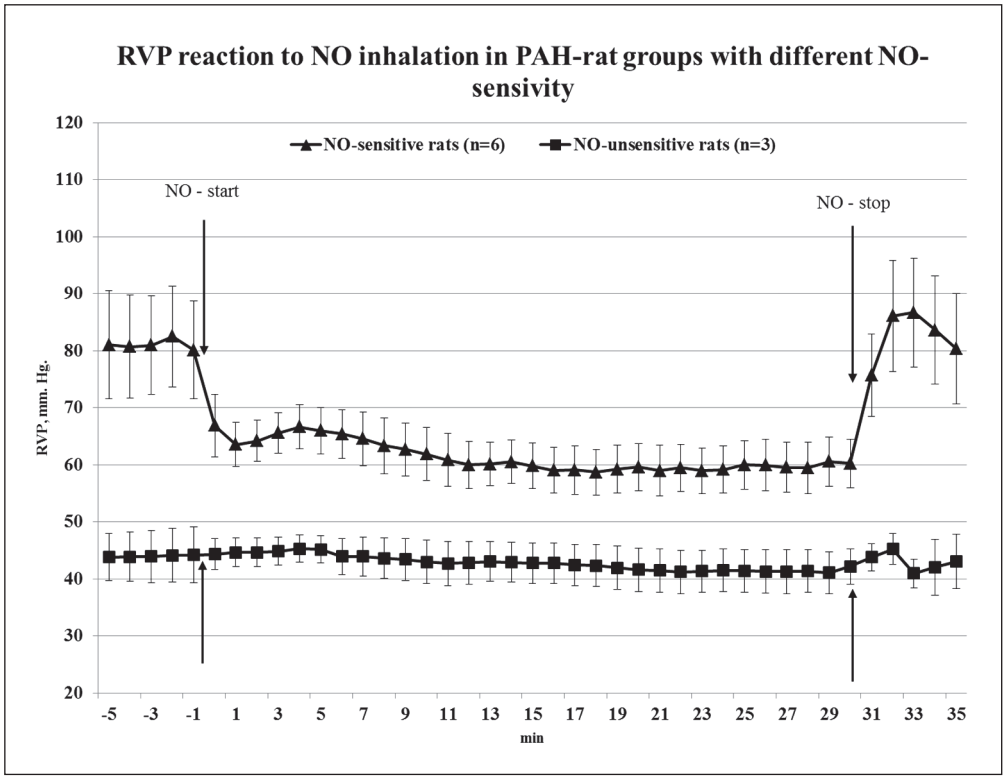


Fig. 3. Effect of NO inhalation (shown by arrows) on RV systolic pressure i n NO-responding (upper curve, n = 6) and NO-nonresponding (lower curve, n = 3) subgroups of monocrotalin-injected rats



are increased lung resistance and thickening of the alveolar walls, they developed within the first week and combined with the deterioration in the diffusion of carbon dioxide [25]. Hypertrophy of the pulmonary arteries occurs through 2 weeks.

Despite an increased RV systolic pressurein hypertrophied RV, themyocardial contractility was significantly reduced. The probable cause may be the defeat of endothelium of coronary vessels, because the whole cardiac output also goes through them. Oxacom reliably raised the RV contractility index in monocrotalin-injected rats, a similar result was observed in chronic heart failure caused by doxorubicin [26].

It is known that the pulmonary tissue is the main host of angiotensin-converting enzyme, it is located in the caveole ofpulmonary endothelium. It was found that in the development of pulmonary hypertension the activity of this enzyme is reduced [19], and thus the action of angiotensin II on arteries of the large circle diminished. This situation is an example of an implementation mechanism for self-regulation of the interaction of the small and big circles.The fact of the influence of high pressure in the pulmonary artery on vascular relaxation in the large circle was opened in 30th years of XX century by V. V. Parinand was named as "Parinreflex", but only now it becomes clear a one of the important mechanisms of this relationship. This reflex is designed to reduce blood inflow to the small circle and thus prevent further pressure rise in it.

Simultaneously a displacement of endothelial NO synthase occurs with reduced production ofnitric oxide [8]. Formation of nitric oxide is also violated due to increased levels of dimethylarginine, preventing arginine absorption necessary for the synthesis of nitric oxide [27]. Numerous studies of the reactivity of pulmonary arteries to vasoconstrictors and vasodilators have shown their variability during the development of monocrotalin damage. A few days after monocrotalin injectiona hyperreactivity of pulmonary arteries to isoproterenol, acethylcholin and nitroprussid changes into hyporeactivityat the second week of introduction [28].The fact that Oxacom is able to induce hypotensive effect in 3 weeks underlines its advantage over nitroprusside. The difference may be due to the presence of continuously elevated levels of nitric oxide, released from DNIC, as well as the effect of glutathione. Glutathione is a known active metabolite binding pirrol metabolite of monocrotalin [29,30], therefore increasing its content in endothelial cells and cardiomyocytes can reduce the toxic effect of alkaloid.

Nitric oxide in our experiments provided ambiguouseffect, but only in two thirds of the experiments. As it turned out, the hypotensive effect of nitric oxide was absent in rats withlesser toxic effect of monocrotalin, accompanied by a smaller rise of the pressure in the small circle. On the contrary, the effect of nitric oxide was well expressed in animals having elevated RV pressure. This result highlights the specificity of nitric oxide therapy. This result is in good agreement with the data of the clinical application of nitric oxide in patients with pulmonary artery hypertension — at the end of the course ofNO inhalation therapy the RV mean pressure according to echocardiography investigation decreased from 96 to 82 mmHg, i. e. by 15 %, as in our experiments. and significant improvement was observed in functional status in patients with FC II–IV, i. e. heavier patients [31]. The absence of hypotensive action of inhaledOxacommost likely is due to the fact that the molecule can not overcome alveolar barrier.

Conclusion.

Monocrotalin-induced lesions of pulmonary endothelium resulted in twice rise in RV systolic pressure reflecting increased pulmonary arterial vessel resistance. In these animals, oxacom, along with its famous prolonged hypotensive effect in the large circle, steadily reduced the RV pressure. Gaseous nitric oxide caused a similar effect. This effect was absent in control animals and those monocrotalin-injected animals which respondedwith only slight RV pressure rise. These results suggest that nitric oxide, as Oxacom, provides hypotensive effect probably only in situations where its level in cells is lower.

Financial support / Финансирование
The study is partially supported by the Russian Foundation of Fundamental Studies, projects № 15–04–06571 a, № 15–04–04355 a. / Работа частично поддержана грантами РФФИ № 15–04–06571, № 15–04–04355 a.

Conflict of interest / Конфликт интересов
The authors declare no conflict of interest. / Авторы заявили об отсутствии конфликта интересов.

Список литературы / References

1. McLaughlin V, Shah S, Souza R, Humbert M. Management of pulmonary arterial hypertension. J Am Coll Cardiol. 2015;65(18):1976–97.

2. Studer S, Gilkin R. Clinical trial designs in PAH: shifting from functional measurements to long-term clinical outcomes. Am J Manag Care. 2014;20(6 Suppl): S115–122.

3. Stenmark K, McMurtry I. Vascular remodeling versus vasoconstriction in chronic hypoxic pulmonary hypertension a time for reappraisal? Circ Res. 2005;97(2):95–8.

4. Voelkel N, Tuder R Hypoxia-induced pulmonary vascular remodeling: a model for what human disease? J Clin Invest. 2000;106(6):733–8.

5. Humbert M, Morrell N, Archer S, Stenmark K, MacLean M, Lang I et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Supplement):S13–24.

6. Firth A, Mandel J, Yuan JJ. Idiopathic pulmonary arterial hypertension. Dis Model Mech. 2010;3(5–6):268–73.

7. Gomez-Arroyo J, Farkas L, Alhussaini A, Farkas D, Kraskauskas D, Voelkel N et al. The monocrotaline model of pulmonary hypertension in perspective. Am J Physiol — Lung Cell Mol Physiol. 2012;302(4): L363–9.

8. Yildiz P. Molecular mechanisms of pulmonary hypertension. Clin Chim Acta. 2009;403(1–2):9–16.

9. Ahmed L, Obaid A, Zaki H, Agha A. Role of oxidative stress, inflammation, nitric oxide and transforming growth factor-beta in the protective effect of diosgenin in monocrotaline-induced pulmonary hypertension in rats. Eur J Pharmacol. 2014;740:379–87.

10. Lakomkin VL, Vanin AF, Imoshin AA, Kapelko VI, Chazov EI. Long-lasting hypotensive action of stable preparations of dinitrosyl iron complexes with thiol-containing ligands in conscious normotensive and hypertensive rats. Nitric Oxide. 2007;16(4):413–418.

11. Chazov EI, Rodnenkov OV, Zorin AV, Lakomkin VL, Gramovich VV, Vyborov ON et al. Hypotensive effect of "oxacom" containing a dinitrosyl iron complex with glutathione: animal studies and clinical trials in healthy volunteers. Nitric Oxide. 2012;26(3):148–56.

12. Гостеев А. Ю., Зорин А. В., Родненков О. В., Драгнев А. Г., Чазов Е. И. Гемодинамическиеэффекты синтетического аналога эндогенных донаторов оксида азота (II)-препарата динитрозильных комплексов железа у больных артериальной гипертонией с неосложненными гипертоническими кризами. Терапевт. арх. 2014;86 (9):49–55. [Gosteev AYu, Zorin AV, Rodnenkov OV, Dragnev AG, Chazov EI. Hemodynamic effects of the synthetic analogue of endogenous nitric oxide (II) donors a dinitrosyl iron complex in hypertensive patients with uncomplicated hypertensive crisis. Ther Arch. 2014;86(9):49–55. In Russian].

13. Hayes B, Will J. Pulmonary artery catheterization in the rat. Am J Physiol. 1978;235(4): H452-H454.

14. Matori H, Umar S, Nadadur R, Sharma S, Partow-Navid R, Afkhami M et al. Genistein, a soy phytoestrogen, reverses severe pulmonary hypertension and prevents right heart failure in rats. Hypertension. 2012;60(2):425–30.

15. Akhavein F, St-Michel E, Seifert E, Rohlicek C. Decreased left ventricular function, myocarditis, and coronary arteriolar medial thickening following monocrotaline administration in adult rats. J Appl Physiol Bethesda Md. 2007;103 (1):287–95.

16. Kolettis T, Vlahos A, Louka M, Hatzistergos K, Baltogiannis G, Agelaki M et al. Characterisation of a rat model of pulmonary arterial hypertension. Hell J Cardiol. 2007;48(4):206–210.

17. Ghodsi F, Will J. Changes in pulmonary structure and function induced by monocrotaline intoxication. Am J Physiol-Heart Circ Physiol. 1981;240(2): H149-H155.

18. Hadri L, Kratlian R, Benard L, Maron B, Dorfmüller P, Ladage D et al. Therapeutic efficacy of AAV1.SERCA2a in monocrotaline-induced pulmonary arterial hypertension. Circulation. 2013;128(5):512–23.

19. Kay J, Keane P, Suyama K, Gauthier D. Angiotensin converting enzyme activity and evolution of pulmonary vascular disease in rats with monocrotaline pulmonary hypertension. Thorax. 1982;37(2):88–96.

20. Piao L, Fang Y, Cadete V, Wietholt C, Urboniene D, Toth P et al. The inhibition of pyruvate dehydrogenase kinase improves impaired cardiac function and electrical remodeling in two models of right ventricular hypertrophy: resuscitating the hibernating right ventricle. J Mol Med Berl Ger. 2010;88(1):47–60.

21. Tanaka Y, Takase B, Yao T, Ishihara M. Right ventricular electrical remodeling and arrhythmogenic substrate in rat pulmonary hypertension. Am J Respir Cell Mol Biol. 2013;49(3):426–36.

22. Pullamsetti S, Kiss L, Ghofrani H, Voswinckel R, Haredza P, Klepetko W et al. Increased levels and reduced catabolism of asymmetric and symmetric dimethylarginines in pulmonary hypertension. FASEB J Off Publ Fed Am Soc Exp Biol. 2005;19(9): 1175–7.

23. Schultze A, Roth R. Chronic pulmonary hypertension — the monocrotaline model and involvement of the hemostatic system. J Toxicol Environ Health Part B. 1998;1 (4):271–346.

25. Reid M, Dunston S, Lamé M, Wilson D, Morin D, Segall H. Effect of monocrotaline metabolites on glutathione levels in human and bovine pulmonary artery endothelial cells. Res Commun Mol Pathol Pharmacol. 1998;99 (1):53–68.

26. Мартынюк Т. В., Наконечников С. Н., Маценко В. П., Чазова И. Е. Ингаляционный оксид азота: клинические эффекты и влияние на профиль провоспалительных маркеров у пациентов с идиопатической легочной гипертензией Рациональная фармакотерапия в кардиологии. 2012;8(4):500–508. [Martynyuk TV, Nakonechnikov SN, Masenko VP, Chazova IE. Inhaled nitric oxide: clinical effects and influence on the profile of in-

flammatory markers in patients with idiopathic pulmonary hypertension. Ratsional'naya Farmakoterapiya v Kardiologii = Rational Pharmacotherapy in Cardiology. 2012;8(4): 500–508. In Russian].

Author information

Aleksandr A. Abramov, Researcher, Laboratory of Experimental Heart Pathology, National Medical Research Centre in Cardiology;

Vladimir L. Lakomkin, Leading Researcher, Laboratory of Experimental Heart Pathology, National Medical Research Centre in Cardiology;

Aleksandr A. Timoshin, Leading Researcher, Laboratory of Physical and Chemical Investigation Methods, National Medical Research Centre in Cardiology;

Elena V. Lukoshkova, Leading Researcher, Laboratory of Experimental Heart Pathology, National Medical Research Centre in Cardiology;

Vladimir V. Ermishkin, Leading Researcher, Laboratory of Experimental Heart Pathology, National Medical Research Centre in Cardiology;

Valeriy I. Kapelko, Head, Laboratory of Experimental Heart Pathology, National Medical Research Centre in Cardiology.

Информация об авторах

Абрамов Александр Александрович — научный сотрудник лаборатории экспериментальной патологии сердца Института экспериментальной кардиологии ФГБУ «НМИЦ кардиологии» Минздрава России;

Лакомкин Владимир Леонидович — ведущий научный сотрудник лаборатории экспериментальной патологии сердца Института экспериментальной кардиологии ФГБУ «НМИЦ кардиологии» Минздрава России;

Тимошин Александр Анатольевич — ведущий научный сотрудник лаборатории физико-химических методов исследования Института экспериментальной кардиологии ФГБУ «НМИЦ кардиологии» Минздрава России;

Лукошкова Елена Владимировна — ведущий научный сотрудник лаборатории экспериментальной патологии сердца Института экспериментальной кардиологии ФГБУ «НМИЦ кардиологии» Минздрава России;

Ермишкин Владимир Вячеславович — старший научный сотрудник лаборатории экспериментальной патологии сердца Института экспериментальной кардиологии ФГБУ «НМИЦ кардиологии» Минздрава России;

Капелько Валерий Игнатьевич — заведующий лабораторией экспериментальной патологии сердца Института экспериментальной кардиологии ФГБУ «НМИЦ кардилогии» Минздрава России.