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Effect of Probiotic Strains, L-Arginine and Carvedilol on Myocardial Infarction Size in Systemic Inflammation in Rats

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ABSTRACT

Aim. To determine the cardioprotective effect of a mixture of probiotic strains of *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium animalis subsp*. *Lactis* (BB-12) in rats with systemic inflammatory response syndrome (SIRS) in comparison with the use of α- and β-adrenoblocker carvedilol and L-arginine, the precursor of nitric oxide (NO).

Materials and methods. Experiments were conducted on male Wistar rats in a model of SIRS including obesity and chemically induced colitis. Probiotic strains (PRK), L-arginine (ARG), and the α- and β-adrenoblocker carvedilol (ADB) were intragastrically administered to animals of the corresponding groups. Myocardial ischemia-reperfusion injury was reproduced in an isolated heart perfusion model. The size of the necrosis zone (SNZ) was determined using histochemistry. The concentration of cytokines in blood plasma was measured using an immunoenzyme technique.

Results. Myocardial SNZ in the group with SIRS modeling was significantly higher than in the control group (45 (38; 48)% and 30 (26; 31)%, $p < 0.05$). In the PRK and ARG groups, the SNZ was 32 (28; 35)% and 35 (26; 36)%, respectively, which was significantly lower compared to the SIRS group ($p < 0.05$). In the ADB group, the SNZ was 40 (31; 48)%, similar to the value in the SIRS group ($p > 0.05$). Hemodynamic parameters in isolated heart did not differ between the groups. The concentration of proinflammatory cytokines and transforming growth factor-β in plasma was significantly higher in the SIRS group than in the control. However,, in the PRK and ARG groups a significant decrease in the levels of some of some cytokines was noted, confirming the presence of an anti-inflammatory effect.

Conclusion. Administration of PRK to rats using the SIRS model caused a decrease in the SNZ. However, of α- and β-adrenoreceptors was not accompanied by a decrease in the SNZ in this model. The amino acid L-arginine had a cardioprotective and anti-inflammatory effect similar to that of the PRK group, which may indicate the unidirectionality of the tested effects.

Keywords: myocardium, ischemia-reperfusion, cardioprotection, systemic inflammatory response syndrome, cytokines, probiotics, nitric oxide

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Влияние пробиотических штаммов, L-аргинина и карведилола на размер инфаркта миокарда у крыс в условиях системного воспаления

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РЕЗЮМЕ

Цель. Определение выраженности кардиопротективного эффекта смеси пробиотических штаммов *Lactobacillus acidophilus* (LA-5) и *Bifidobacterium animalis* subsp. *Lactis* (BB-12) у крыс с синдромом системного воспалительного ответа (ССВО) в сравнении с применением α- и β-адреноблокатора карведилола и предшественника оксида азота (NO) L-аргинина.

Материалы и методы. Эксперименты выполнены на самцах крыс стока Вистар на модели ССВО, включающей ожирение и химически индуцированный колит. Животным соответствующих групп внутрижелудочно вводили пробиотические штаммы (ПРК), L-аргинин (АРГ) и α- и β-адреноблокатор карведилол (АДБ). Ишемическое-реперфузионное повреждение миокарда воспроизводили на модели перфузии изолированного сердца. Размер зоны некроза (РЗН) определяли гистохимически. Концентрацию цитокинов в плазме крови оценивали иммуноферментным методом.

Результаты. Размер зоны некроза миокарда в группе с моделированием ССВО был значимо выше, чем в контрольной группе (45 (38;48)% и 30 (26;31)%, $p < 0,05$). В группах ПРК и АРГ РЗН составил 32 (28;35)% и 35 (26;36)%, что значимо меньше по сравнению с группой ССВО ($p < 0,05$). В группе АДБ РЗН составил 40 (31;48)%, не отличаясь от значения в группе ССВО ($p > 0,05$). Гемодинамические показатели изолированного сердца не отличались между группами. В группе ССВО концентрация провоспалительных цитокинов и трансформирующего фактора роста-β в плазме крови была значимо выше, чем в контроле. При этом в группах ПРК и АРГ отмечено значимое уменьшение уровней некоторых цитокинов, подтверждающее наличие противовоспалительного эффекта.

Заключение. Введение ПРК у крыс на модели ССВО вызвало уменьшение РЗН. При этом блокада α- и β-адренорецепторов не сопровождалась уменьшением РЗН на данной модели. Аналогичным группе ПРК кардиопротективным и противовоспалительным действием обладала аминокислота L-аргинин, что может свидетельствовать об однонаправленности эффекта протестированных воздействий.

Ключевые слова: миокард, ишемия-реперфузия, кардиопротекция, синдром системного воспалительного ответа, цитокины, пробиотики, оксид азота

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией данной статьи.

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INTRODUCTION

The increased risk of cardiovascular diseases in metabolic syndrome (MS) and its individual components is confirmed by large-scale clinical observations. According to the World Health Organization, in 2022, every 8th person in the world was obese, and 2.5 billion people over over the age of 18 were overweight. The prevalence of MS in the general population varies from 14 to 24%, depending on the socioeconomic status of the country and region, with the highest prevalence in the United States.

According to 2022 data, the number of overweight children under 5 years of age in Africa has increased by 23% since 2000, while in Asian countries almost half of children of the same age are overweight or obese [1]. These data clearly indicate that experimental research in the field of cardioprotection, i.e. the development of ways to protect the myocardium from ischemia-reperfusion injury (IRI), should be conducted on clinically relevant models that include pathology in the form of visceral obesity, type 2 diabetes mellitus, and arterial hypertension [2].

Considering that systemic inflammation is the pathogenic factor that unifies various MS components, we have developed and validated an experimental model of systemic inflammatory response syndrome (SIRS) in rats, which includes the formation of obesity caused by a high-fat diet chemically induced colitis and the administration of antimicrobial drugs [3, 4]. Using this SIRS model in experiments on an isolated perfused heart and on a model of coronary occlusion myocardial infarction, the literature data were confirmed that systemic inflammation is accompanied by significant changes in the qualitative composition of the intestinal microbiota and a decrease in myocardial resistance to IRI [5, 6].

The effect of proinflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1 β (IL-1β), on the heart is the most important mechanism contributing to the increase in infarction size in SIRS. These cytokines negatively affect the state of cardiac microcirculatory bloodstream, increasing microvascular permeability and inducing the expression of adhesion molecules on endothelium, increase the manifestations of myocardial oxidative, and trigger apoptosis of cardiac myocytes [7]. In this regard, an urgent task is to search for new safe and effective ways to affect the mechanisms of systemic inflammation in order to reduce its negative effects on various processes, including myocardial IRI.

One of such ways is the modulation of the intestinal microbiota composition through various interventions including the use of antibiotics and probiotics, as well as the transplantation of transplantation of intestinal microflora. In recent years, a number of studies have shown that changes in the intestinal microbiota composition are accompanied by an increase in myocardial resistance to IRI both in healthy animals and in those with a concomitant pathology [8, 9]. The studies of our research group have demonstrated that administration of a mixture of probiotic strains of lactobacilli and bifidobacteria to rats with SIRS leads to a decrease in the concentration of proinflammatory cytokines in the blood, is also accompanied by a decrease in the infarction size in the model of global ischemia-reperfusion of an isolated heart [10].

The possible mechanisms of anti-inflammatory and cardioprotective effects of the intestinal microbiota are of particular interest, the study of which is currently at the very initial stage. Some data suggest that optimization of the intestinal microflora composition leads to a decrease in paracellular permeability of intestinal epithelium and a decrease in the effect of bacterial translocation, which, in turn, reduces the stimulation

of innate and adaptive immunity. The direct effect of metabolites produced by certain representatives of the intestinal microbiocenosis on cardiomyocytes with the activation of intracellular signaling pathways of cardioprotection is not excluded [5].

Nitrogen monoxide (NO) is of great importance in the regulation of the inflammatory response; which has an anti-inflammatory effect in physiological concentrations concentrations, but demonstrates pronounced pro-inflammatory properties when its production is locally enhanced by inducible isoforms of NO synthase [11]. It is important to note that the general enhancement of NO production during administration of its pharmacological donors and its precursor L-arginine has a cardioprotective effect effect in healthy animals [12], although blockade of endogenous NO synthesis with the methyl ester L^{ω} -nitro-N-arginine does not eliminate the effect of myocardial ischemic preconditioning [13]. The influence of the sympathetic nervous system is also significant, as its prolonged activation has a pro-inflammatory effect and is considered as one of the leading mechanisms of chronic heart failure progression [14].

Based on these data, it was assumedthat the use of adrenoblockers and substances that enhance NO production may have a cardioprotective effect in in SIRS conditions and have a unidirectional effect with the use of PRK. The aim of the present study was to determine the cardioprotective effect of a mixture of probiotic strains *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium animalis subsp. Lactis* (BB-12) in rats with SIRS in comparison to the use of α- and β-adrenoblocker carvedilol and NO precursor L-arginine.

MATERIALS AND METHODS

The experiments were performed on male Wistar rats of improved conventional status weighing 322 ± 25 g in accordance with the. The for the use of animals was reviewed and approved by the Committee for the Control of the Care and Use of Laboratory Animals of the Almazov National Medical Research Center of the of SIRS was described in detail earlier [3].

Animals were randomly assigned to one of five groups (n = 9 in each group): 1) control (CTR) group, in which which rats received standard food and drinking water *ad libitum*; 2) systemic inflammatory response syndrome (SIRS) group included animals with primary visceral obesity induced by a high fat and carbohydrate diet, under combined anesthesia (zoletil 20 mg/kg i/m, isoflurane 1.5%), 1 ml of a mixture of 3% acetic acid solution and 3% ethanol was injected once rectally to induce acute colitis. Starting that day, the same animals were intragastrically administered a mixture of antimicrobial drugs (AMD) (amoxicillin, metronidazole, and clarithromycin) in 1 ml normal saline solution (NS) at a daily dose of 15 mg of each AMD per rat for 3 days and 1 ml of NS for 5 days; 3) PRK group in which rats that underwent the procedures described for the previous group were additionally intragastrically administered 1 ml of a solution of a mixture of probiotic strains *Lactobacillus acidophilus (LA-5)* and *Bifidobacterium animalis subsp. lactis (BB-12)* at a dose of 10^8 CFU per animal during the last 8 days of the experiment; 4) ARG group – during the last 8 days of the experiment, instead of the probiotic mixture, 50 mg of L-arginine in 1 ml of NS per animal administered intragastrically; 5) ADB group – during the last 8 days of the experiment, 2 mg of α- and β-adrenoreceptor blocker carvedilol orally administered in 1 ml of NS per animal. The doses and modes of administration to rats in the ARG and ADB groups were selected on the basis of the literature [15, 16].

One day before the end of the experiment, whole blood (1.5 ml) was drawn from the large saphenous vein for hematological and immunological analysis in rats under short-term isoflurane anesthesia. The number of erythrocytes, leukocytes, and platelets in blood was determined on an automated veterinary hematology 3-differential analyzer (URIT-3000 Vet Plus, URIT Medical Electronic, China). The levels of TNF-α, IL-1β, IL-6 and transforming growth factor-β (TGF-β) in blood plasma were evaluated by immunoenzyme method (MR-96A, Mindray, China).

Global ischemia-reperfusion of the isolated heart was modeled on the Langendorff apparatus. For this purpose, the animals were anesthetized with isoflurane, fixed on the operating table, and a wide bilateral transdiaphragmatic incision was made to provide access to the heart. The heart was removed and its through the aorta with a Krebs-Henseleit-Henseleit buffer with a hydrostatic pressure of 80 mm Hg at 37°C. Immediately after the start of perfusion, a polyethylene balloon connected by a flexible cannula to a pressure sensor and a software and hardware complex for recording hemodynamics (PhysExp Gold, Cardioprotekt, Russia) was placed into the left ventricle through the mitral valve.

The duration of global ischemia was 30 min, reperfusion – 90 min. After 15 minutes of stabilization

at baseline, as well as at 15, 30, 45, 60, 75, and 90 minutes of reperfusion, the following values were recorded: left ventricular systolic pressure (LVSP, mm Hg), heart rate (HR, bpm), coronary flow (CF, ml/min). After completion of reperfusion, the heart was cut into into five 2-mm-thick transverse sections which were incubated at 37°C in 1% triphenyltetrazolium chloride (TTC) solution for 15 minutes. The sections were then photographed with a digital camera connected to a stereomicroscope, and the images were coded. The researcher, who was not familiar with image coding procedure, performed a planimetric assessment of the nectrotic zone size zone size (NZS) using ImageJ program. The NZS was expressed as the percentage of the area area of TTC-negative areas averaged over five slices.

Statistical processing of experimental data was performed using the STATISTICA 12.0 software package. The Kolmogorov–Smirnov test was used to determine the distribution pattern. Due to the different distribution pattern in the groups, preliminary statistical analysis was performed on the basis of the nonparametric Kruskal–Wallis (H test) to detect statistically significant differences between samples, followed by pairwise comparison using the Mann–Whitney *U* test and appropriate adjustments in the multiple comparison program. Differences determined by the program for each dimension were considered statistically significant. The tables show the the values of the median (*Me*), as well as the lower and upper quartiles (25%;75%).

RESULTS

Clinical blood counts showed a significant increase in leukocytes, platelets, including large platelets in the SIRS group compared to the CTR group (SSD, Table 1). There was a trend toward a decrease in leukocyte count in the PRK group compared to the SIRS group, and there was a significant decrease in large platelets (SSD, Table 1). In the ARG group, there was a significant decrease in the number of large platelets (SSD, Table 1). The parameters of clinical blood count in the ADB group did not differ from those in the SIRS group.

Table 1

Hematologic Parameters, *Me* (25%;75%)

Analyte	Group				
	CTR	SIRS	PRK	ARG	ADB
Leukocytes, ×109 /L, $p = 0.001$	3.4# (3.1;3.8)	5.7* (4.8;6.5)	4.0 (3.5;4.2)	4.0 (3.8;5.5)	5.9* (4.8;8.3)
Erythrocytes, $\times 10^{12}$ /L, $p = 0.2679$	8.0 (7.1;8.7)	8.2 (7.8;9.2)	7.4 (7.1;9.2)	9.8 (8.0;10.1)	8.5 (7.7;9.3)
Platelets, $\times 10^{9}$ /L, $p = 0.0344$	546# (515;596)	781* (693;925)	582 (548;770)	631 (608;806)	752 (503;899)
Large platelets, $\times 10^{9}$ /L, $p = 0.0008$	39# (35;44)	67* (62;69)	45# (40;51)	47# (44;50)	55 (40;64)

Here and in Table 2: CTR – control; SIRS – systemic inflammatory response syndrome; PRK – SIRS and *LA-5* and *BB-12* mixture; ARG – SIRS and L-arginine; ADB – SIRS and carvedilol; *p* – the level of significance.
* statistically significant difference (SSD) in relation to CTR group; # SSD in relation to SIRS group.

When analyzing the level of cytokines in the blood plasma, it was found that the concentrations of TNF-α were significantly higher and IL-1β, IL-6, and TGF-β in the SIRS group were statistically significantly higher (by 64, 41, 43, and 50%, respectively) than in the control (Table 2). The administration of probiotics to the animals was accompanied by a significant decrease in the levels of IL-1β and IL-6 compared to the SIRS group (by 50 and 36%, respectively, Table 2).

The IL-1β concentration was lower in the ARG group than in the SIRS group (SSD, Table 2). No statistically significant changes were observed in the ADB group in relation to the SIRS group.

Table 2

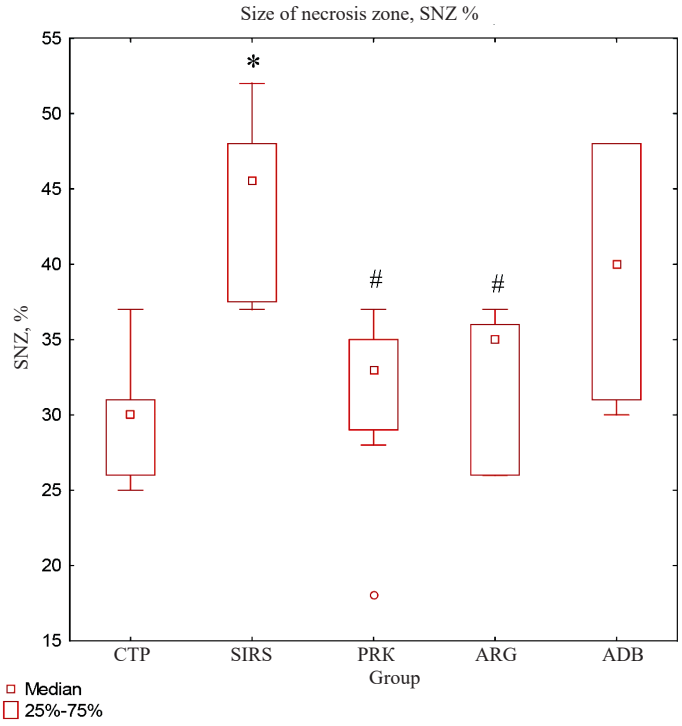
Levels of Cytokines in Plasma, *Me* (25%;75%)

Analyte	Group				
	CTR	SIRS	PRK	ARG	ADB
TNF-α, pg/mL, $p = 0.0393$	1.3 (1.0;1.6)	1.8 (1.5; 3.0)	1.2# (0.4; 1.5)	0.6 (0.5; 1.9)	1.0 (0.9; 3.1)
IL-1β, pg/mL, $p = 0.0004$	80# (70; 90)	120* (113; 150)	80# (62; 95)	77# (66; 78)	90 (80; 100)
IL-6, pg/mL, $p = 0.0007$	5.6# (4.7; 6.0)	8.0* (7.5; 8.6)	5.8# (4.9; 6.2)	6.2 (4.7; 7.0)	7.0 (5.3; 7.3)
TGF-β, pg/mL, $p = 0.0013$	26# (21; 30)	39* (39; 43)	30 (25; 41)	31 (30; 49)	48* (35; 54)

* SSD in relation to the CTR group; # SSD in relation to the SIRS group.

Hemodynamic parameters (left ventricular systolic pressure, heart rate, and coronary flow) at baseline, 15, 30, 45, 60, 90, and 120 minutes after 30 minutes of global ischemia were not statistically different between groups.

The myocardial SNZ in the SIRS modeling group was significantly higher than in the control group (45 (38; 48)% and 30 (26; 31)%, (SSD, Fig.). In the PRK and ARG groups, the SNZ was 32 (28; 35)%, and 35 (26; 36)%, which was significantly lower compared with the SIRS group (SSD, Fig.), whereas in the ADB group, the SNZ was 40 (31; 48)%, which was not significantly different from its value in the SIRS group (Fig.).



SNZ %: F(4; 35) = 8,2786; p = 0,00008; KW-H(4; 40) = 18,5426; p = 0,0010

Figure. Size of myocardial necrosis zone, *Me* (25%;75%): CTR – control; SIRS – systemic inflammatory response syndrome; PRK – SIRS and a mixture of *LA-5* and *BB-12*; ARG – SIRS and L-arginine; ADB – SIRS and carvedilol; p – the level of significance. * SSD in relation to CTR group, # SSD in relation to SIRS group

DISCUSSION

The study confirmed the fact of an increased myocardial infarction size in SIRS caused by primary obesity in combination with chemically induced colitis. The presence of SIRS was verified by increased leukocyte and platelet counts and a significant increase in the concentration of pro-inflammatory cytokines in the blood. Recently, new experimental evidence has been obtained that the presence of acute inflammation with hypercytokinemia leads to a decreased myocardial resistance to IRI. In particular, in the model of dextran sulfate-induced inflammatory bowel disease in mice, it was shown that the severity of myocardial IRI is significantly increased in the presence of systemic inflammation, with IL-6 being one of the mediators of this effect [17]. It is hypercytokinemia that is considered as the leading mechanism of myocardial IRI resistance reduction in SIRS, since TNF-α and IL-1β provoke a number of cardionegative effects, including initiation of cardiomyocyte apoptosis and enhancement of cardiomyocyte oxidative damage.

The conducted experiments demonstrated the infarct-limiting effect of probiotic therapy with *Lactobacillus acidophilus* (LA-5) and *Bifidobacterium animalis subsp. Lactis* (BB-12) in animals with SIRS. However, the infarction size in the group of animals receiving probiotics was not significantly different from the corresponding value in the control. On the other hand, probiotics administration was accompanied by a decrease in the level of TNF-α and IL-1β, which allows us to associate the effect of probiotic cardioprotection with the anti-inflammatory effect of the introduced bacteria and/or the secondary changes in the general microbial landscape of the intestine induced by them. It is known that a number of probiotic strains have the ability to normalize the increased permeability of the intestinal mucosa

by increasing mucus production, preventing the degradation of tight junctions between enterocytes, stimulation of anti-inflammatory mechanisms in the form of activation of T-regulators, etc. [18].

Although these effects have been most fully studied in relation to the manifestations of inflammation directly in the intestinal wall in colitis, in the context of this study, the reduction of manifestations of systemic inflammation is equally important. Mechanisms of probiotic cardioprotection may include other signaling pathways associated with direct activation of cardiomyocyte receptors by bioactive substances produced by intestinal microflora and entering the systemic bloodstream. This assumption is supported by data showing that cardioprotection in SIRS is formed only when live bacteria of *Lactobacillus delbrueckii D5* strain are used and is lost when pasteurized culture is administered to animals [19]. Short-chain fatty acids (acetic, propionic and butyric acids) interacting with free fatty acid receptors 3 (FFAR3) found in the mammalian heart [20], as well as bile acids and their derivatives signaling through nuclear farnesoid X receptor (FXR) and G-protein-coupled membrane receptor of bile acids 1 (TGR5) [21] are claimed to play the role of such cardioprotective signals.

Obviously, the study of the mechanisms of probiotic-mediated cardioprotection is at the initial stage and requires the use of both pharmacological agents blocking certain targets and animal biomodels not expressing or hyperexpressing the corresponding proteins. At the same time, when using appropriate pharmacological tools, it is necessary to evaluate the presence of their own effect on myocardial IRI and its targeting. In the present study, the effects of two substances with anti-inflammatory and cardioprotective effects, the NO precursor L-arginine and the α- and β-adrenoreceptor blocker carvedilol, were tested in a.

Unlike carvedilol, L-arginine was found to have a significant cardioprotective effect in animals with SIRS, which was associated with a decrease in in the level of IL-1β in the blood plasma and the number of large platelets. Exogenous administration of L-arginine can lead to an increase in NO formation in the body, although the presence of this effect was not shown in all studies and seems to depend on the mode of administration, dose, and other factors [22]. This study did not measure the level of NO metabolites in the blood, which is one of the limitations. Nevertheless, there is reason to believe that the observed cardioprotective effect of L-arginine is associated with an increase in NO production because previously a number of studies on healthy animals showed the administration of L-arginine, as well as NO donators sodium nitroprusside and S-nitroso-N-acetylpenicillamine, was accompanied by an improvement in postischemic recovery of left ventricular contractility and a decrease in the size of myocardial infarction [12, 23]. The mechanism of cardioprotective effect of NO is associated with stimulation of guanylate cyclase, increased production of cGMP in cardiomyocytes and activation of protein kinase G, which, in turn, provides opening of ATP-sensitive mitochondrial potassium channels [24].

Activation of the sympathetic nervous system is traditionally regarded as an important pro-inflammatory mechanism, which is realized both by direct activation of immune cells through stimulation of adrenoreceptors and indirectly through activation of the renin-angiotensin system. In this regard, the use of β-adrenoblockers represents the basis of modern therapy of chronic cardiac insufficiency, aimed at blockade of maladaptive activation of neurohumoral systems. The question about the presence and severity of infarct-limiting effect of β-adrenoblockers is more complicated because most studies have not shown a significant effect of this group of drugs on the infarction size and LV ejection fraction [25].

However, there is evidence that adenoblockers acting on both β- and α-adrenoreceptors may have advantages over selective β-adrenoblockers. For example, the CAPRICORN study found that the α- and β-adrenoreceptor blocker carvedilol improved outcomes in patients with acute myocardial infarction and LV dysfunction compared with a selective β_1 -adrenoreceptor blocker [26]. It is noteworthy that carvedilol has a number of additional pleiotropic properties that enhance its cardio- and vasoprotective potential. Such properties include a pronounced antioxidant effect of carvedilol, realized due to the presence of carbazole group in its composition, and endothelioprotective effect.

In particular, antihypertensive and antiremodeling effects of carvedilol are eliminated by administration of NO synthase blocker nitro-N-arginine, which indicates the important role of NO in the mechanism of action of the drug [27, 28]. These prerequisites allowed us to consider carvedilol as a potential cardioprotective agent having common mechanisms of action with L-arginine. Nevertheless, carvedilol in the used dosage did not have cardioprotective effect in animals with SIRS.

CONCLUSION

Unlike carvedilol, the α- and β-adrenoreceptor blocker, L-arginine, the precursor of NO, has a cardioprotective effect in the presence of systemic inflammation. The infarct-limiting and anti-inflammatory effect of probiotics based on lacto- and bifidobacteria has a similar direction to L-arginine.

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