

# GEORGIAN MEDICAL NEWS

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии  
საქართველოს სამედიცინო სიახლენი

## GEORGIAN MEDICAL NEWS

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**GMN: Georgian Medical News** is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

**GMN: Медицинские новости Грузии** - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

**GMN: Georgian Medical News** – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

## WEBSITE

[www.geomednews.com](http://www.geomednews.com)

## К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html). В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

**При нарушении указанных правил статьи не рассматриваются.**

## REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html)  
[http://www.icmje.org/urm\\_full.pdf](http://www.icmje.org/urm_full.pdf)

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned  
Requirements are not Assigned to be Reviewed.**

## ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

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## PRO-INFLAMMATORY INTERLEUKINS AND OXIDATIVE IMBALANCE IN L-NAME-INDUCED HYPERTENSION: COMPARATIVE EFFECTS OF B-BLOCKERS

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### Abstract.

**Background:** Hypertension is a multifactorial condition characterized by vascular dysfunction, oxidative stress, and immune activation. Pro-inflammatory cytokines, particularly IL-6, IL-17, and TNF- $\alpha$ , contribute to inflammatory processes in hypertension; therefore, they should be considered together with nitric oxide (NO) deficiency and oxidative imbalance when interpreting arterial pressure changes.

**Objective:** To evaluate the association between pro-inflammatory interleukins, nitric oxide metabolites, oxidative status, and arterial pressure in an experimental model of hypertension, and to compare the effects of  $\beta$ -blockers.

**Methods:** Hypertension was induced in 70 male Wistar rats by chronic administration of N $\omega$ -nitro-L-arginine methyl ester (L-NAME, 40 mg/kg/day, intraperitoneally) for 8 weeks. Animals were randomized into seven groups (n = 10/group): intact control, L-NAME for 4 weeks, L-NAME for 8 weeks, and four L-NAME +  $\beta$ -blocker treatment groups receiving nebivolol (0.5 mg/kg/day), propranolol (0.1 mg/kg/day), metoprolol (3 mg/kg/day), or carvedilol (2 mg/kg/day) by oral gavage during weeks 5–8. Arterial pressure was measured using a noninvasive tail-cuff method. Serum IL-6, IL-17, and TNF- $\alpha$  were quantified by ELISA. Nitric oxide metabolites and total antioxidant activity (TAA) were assessed using the Griess reaction and DPPH assay.

**Results:** L-NAME administration resulted in a time-dependent increase in arterial pressure, accompanied by reduced NO metabolites and TAA and increased interleukin levels.  $\beta$ -blockers attenuated these changes to varying degrees. Nebivolol and carvedilol produced greater improvements in arterial pressure, NO metabolites, TAA, and interleukin levels compared with propranolol and metoprolol.

**Conclusion:** Chronic NOS inhibition was associated with hypertension and concurrent alterations in inflammatory and oxidative parameters.  $\beta$ -blockers differ in their modulatory effects, with nebivolol and carvedilol demonstrating greater overall efficacy. These findings reflect associations rather than causal mechanisms and support further investigation into integrated therapeutic strategies.

**Key words.** Hypertension, interleukins, IL-6, IL-17, TNF- $\alpha$ , nitric oxide, oxidative stress,  $\beta$ -blockers.

### Introduction.

Hypertension is a complex cardiovascular condition and a leading cause of global morbidity and mortality [1,2]. The pathophysiology of hypertension involves a dynamic interplay among genetic susceptibility, neurohumoral dysregulation, endothelial dysfunction, renal sodium handling, and vascular inflammation [3–6].

This complexity is reflected in the variability of responses to antihypertensive therapies, as well as in the distinct molecular and cellular characteristics observed across experimental models of hypertension [3,7]. The interaction between the renin–angiotensin system (RAS), the sympathetic nervous system, oxidative stress pathways, and immune mechanisms significantly contribute to the development and progression of hypertension, often leading to early target-organ damage [8–10].

Beyond its classical characterisation as a hemodynamic disorder, growing evidence highlights the critical role of immune dysregulation and chronic low-grade inflammation in the pathogenesis of hypertension [10,11]. Among inflammatory mediators, pro-inflammatory cytokines—particularly IL-6, TNF- $\alpha$ , and IL-17 - play a central role in regulating immune responses and contributing to vascular dysfunction, remodelling, and sustained elevation of blood pressure.

Elevated levels of IL-6, TNF- $\alpha$ , and IL-17 have been consistently reported in patients with hypertension and in experimental models, including spontaneously hypertensive rats and angiotensin II-induced hypertension [11–13]. These interleukins contribute to oxidative stress, endothelial dysfunction, vascular smooth muscle proliferation, and sympathetic nervous system activation, thereby maintaining hypertensive states [10,12]. IL-6 has been shown to enhance angiotensin II receptor expression, amplifying vasoconstriction, while IL-17 promotes vascular inflammation and immune cell infiltration into the vascular wall [13,14].

The N $\omega$ -nitro-L-arginine methyl ester (L-NAME)-induced hypertension model, based on chronic administration of L-NAME, a nitric oxide synthase inhibitor, is widely used to study endothelial dysfunction, vascular remodelling, and immune activation. Reduced nitric oxide bioavailability in this model leads to increased oxidative stress and elevated blood pressure, closely resembling key features of human essential hypertension [4,15]. Importantly, L-NAME-induced hypertension is associated with increased levels of pro-inflammatory interleukins, including IL-6 and IL-1 $\beta$ , along with immune cell infiltration into vascular tissues [16].

In this context,  $\beta$ -adrenergic blockers ( $\beta$ -blockers) are not only effective antihypertensive agents but also modulators of inflammatory pathways. Increasing evidence suggests that  $\beta$ -blockers can influence the production of specific pro-inflammatory interleukins rather than acting broadly on all cytokines. Experimental and clinical studies have demonstrated that propranolol, metoprolol, carvedilol, and nebivolol can reduce circulating levels of IL-6, TNF- $\alpha$ , and IL-17, alongside improvements in blood pressure regulation [17–20].

For instance, metoprolol and propranolol have been shown to decrease IL-6 expression in cardiovascular disease models [18],

while nebivolol exhibits anti-inflammatory effects associated with reduced IL-6 levels and improved endothelial function [20]. Carvedilol has also been reported to inhibit inflammatory signalling pathways, including NLRP3 (NOD-like receptor family pyrin domain-containing 3) inflammasome activation, thereby modulating IL-6 production [21]. Furthermore, recent findings by Kajaia et al. (2025) [22] demonstrated that  $\beta$ -blockers differentially modulate interleukin release through interactions with adrenergic and immune signalling pathways, further supporting their immunomodulatory role.

The anti-inflammatory effects of  $\beta$ -blockers vary depending on receptor selectivity, lipophilicity, and additional pharmacological properties. Selective  $\beta_1$ -blockers (e.g., metoprolol), non-selective agents (e.g., propranolol), and vasodilatory  $\beta$ -blockers (e.g., nebivolol, carvedilol) exhibit distinct capacities to regulate pro-inflammatory interleukin signalling, highlighting the importance of drug-specific mechanisms in therapeutic outcomes.

Therefore, this study specifically focuses on pro-inflammatory cytokines (IL-6, TNF- $\alpha$ , and IL-17) and aims to:

- (i) clarify their role in the development of experimental hypertension;
- (ii) evaluate the effects of different  $\beta$ -blockers on interleukin imbalance and blood pressure regulation.

## Materials and Methods.

**Animals and Experimental Design:** The study was conducted on 70 adult male Wistar rats (200-250 g), obtained from the Animal Facility of Tbilisi State Medical University (Tbilisi, Georgia). Male animals were used to minimize potential sex-related variability in blood pressure regulation, inflammatory responses, oxidative stress parameters, and hemorheological characteristics.

Animals were acclimatised to laboratory conditions for 7 days before the start of the experiment and housed in standard polypropylene cages (4-5 rats per cage) under controlled environmental conditions (temperature  $22\pm 2^\circ\text{C}$ , relative humidity 50-60%, 12 h light/12 h dark cycle). Standard laboratory chow and tap water were provided ad libitum throughout the study.

The sample size was determined based on preliminary data and a power analysis to ensure adequate statistical power ( $\geq 80\%$ ) to detect significant intergroup differences at  $\alpha = 0.05$ . Animals were allocated to experimental groups after acclimatization using random assignment, with 10 animals included in each group. The same housing, feeding, handling, and measurement conditions were maintained across all groups to reduce procedural bias.

All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and complied with the principles of the 3Rs (Replacement, Reduction, and Refinement). The study protocol, including L-NAME administration,  $\beta$ -blocker treatment, blood pressure measurements, blood collection, anaesthesia, and euthanasia procedures, was approved by the Ethics Committee of Tbilisi State Medical University (approval date: July 26, 2022).

## Induction of Experimental Hypertension:

Experimental arterial hypertension was induced by chronic

inhibition of nitric oxide synthase using N $\omega$ -nitro-L-arginine methyl ester (L-NAME; Sigma-Aldrich, USA). L-NAME was administered intraperitoneally at a dose of 40 mg/kg/day, freshly dissolved in physiological saline, for either 4 weeks (intermediate hypertensive group) or 8 weeks (established hypertensive and treatment groups).

Although oral administration of L-NAME is more commonly used in experimental models, intraperitoneal administration was selected to ensure precise, reproducible dosing and to avoid variability associated with voluntary intake via drinking water. This approach has been previously validated as an effective method for inducing nitric oxide deficiency and stable hypertension in experimental animals [7,15].

## $\beta$ -Blocker Treatment:

Animals were randomly assigned to seven experimental groups ( $n = 10$  per group) after the acclimatisation period. In treatment groups, L-NAME administration was continued throughout the entire 8-week experimental period, while  $\beta$ -blockers were administered concomitantly during weeks 5-8. All  $\beta$ -blockers were administered once daily by oral gavage at the same time each day, and treatment lasted 4 weeks (Table 1). Before the experiment, animals were habituated to handling and gavage procedures to minimise stress-related variability.

The selected doses were based on previously published experimental studies demonstrating antihypertensive, anti-inflammatory, and antioxidant efficacy, with no evidence of toxicity [17-21]. Because  $\beta$ -blockers differ substantially in receptor selectivity, pharmacokinetics, pharmacodynamics, and pleiotropic properties, different doses were used for each agent. Therefore, the results should be interpreted within a pharmacological context rather than as a direct dose-equivalent comparison of efficacy.

## Blood Pressure Measurements:

Systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were measured using a non-invasive tail-cuff plethysmography system (PhysioSuite, Kent Scientific, USA).

Before data collection, animals were acclimatized to the restraint and measurement procedures for five consecutive days to minimise stress-induced variability. During measurements, rats were maintained at  $30\text{-}32^\circ\text{C}$  to ensure adequate tail blood flow. Each blood pressure value represented the mean of three consecutive stable measurements obtained during the same session.

## Blood Collection and Sample Processing:

At the end of the experimental period (weeks 4 and 8), animals were fasted overnight and anaesthetized with ketamine (80 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.).

Following induction of deep anaesthesia, blood samples were collected by abdominal aorta puncture. Euthanasia was subsequently performed by exsanguination under anaesthesia, followed by cervical dislocation to ensure death.

Approximately 3-5 mL of blood was collected from each animal. Samples designated for serum analyses were transferred into sterile tubes without anticoagulant, allowed to clot at room temperature for 20-30 min, and centrifuged at 3000 rpm for 10 min at  $4^\circ\text{C}$ . The obtained serum was aliquoted and stored at  $-80^\circ\text{C}$  until biochemical analysis.

### Serum cytokine levels (IL-6, IL-17, and TNF- $\alpha$ ):

Serum concentrations of IL-6, IL-17, and TNF- $\alpha$  were determined using commercially available rat ELISA kits (FineTest, China) according to the manufacturer's instructions. All samples and standards were analysed under the same assay conditions; concentrations were calculated from standard calibration curves and expressed in pg/mL. Optical density was measured using a microplate reader, and assay results were interpreted only when standard-curve performance was acceptable according to the kit instructions.

### Determination of Nitric Oxide Metabolites (NOx) Levels in Blood:

The levels of nitrogen oxides (NOx) in blood samples were determined using a modified Griess method [23].

This method indirectly quantifies total nitric oxide by measuring its stable metabolites - nitrite (NO<sub>2</sub><sup>-</sup>) and nitrate (NO<sub>3</sub><sup>-</sup>) - after reducing nitrate to nitrite.

The first step involved deproteinization of serum samples. To achieve this, 100  $\mu$ L of blood serum was mixed with an equal volume of 0.3 M sodium hydroxide (NaOH) and incubated at room temperature for 5 minutes to ensure thorough mixing. Following this, 100  $\mu$ L of a 5% zinc sulfate (ZnSO<sub>4</sub>) solution was added to the mixture. After additional vigorous mixing, the solution was incubated at room temperature for another 5 minutes.

Next, the mixture was centrifuged at 3,000 rpm for 15 minutes at 4°C to separate the components, and 100  $\mu$ L of the clear supernatant was carefully collected. This aliquot was then combined with 200  $\mu$ L of freshly prepared Griess reagent.

The Griess reagent consisted of 0.25% vanadium chloride (VCl<sub>3</sub>), 0.1% sulfanilamide, and 0.05% N-(1-naphthyl)-ethylenediamine (NED) (Sigma-Aldrich), all dissolved in 0.5 M hydrochloric acid (HCl). A reagent blank was prepared similarly, using 100  $\mu$ L of distilled water in place of the blood serum sample.

The resulting mixture was incubated at 37°C for 30 minutes, after which the absorbance was measured at 540 nm using a microplate reader (Multiskan GO, Thermo Fisher Scientific, Finland).

A standard calibration curve was generated using sodium nitrite (NaNO<sub>2</sub>) at concentrations ranging from 1 to 100  $\mu$ M. NOx results were expressed as concentration units (mM) and were reported as mean  $\pm$  SE with 95% confidence intervals for each experimental group.

### Oxidative stress assessment:

The intensity of oxidative stress in blood samples was assessed according to the integrative indicator of total activity of the non-

enzymatic antioxidant system.

Total antioxidant activity (TAA) was used as an integrative indicator of systemic antioxidant capacity, reflecting the cumulative effect of non-enzymatic antioxidants present in serum. Although TAA does not provide information on specific antioxidant enzymes such as superoxide dismutase, catalase, or glutathione peroxidase, it is widely used in experimental studies as a global marker of redox status and oxidative balance [24].

TAA was determined in deproteinized blood serum using the 2,2-diphenyl-1-picrylhydrazyl (DPPH)-scavenging assay, adapted by Chrzczanowicz et al. [25]. Blood serum samples (1 mL) were deproteinized by adding 3 mL of acetonitrile and centrifuging them for 10 min (4°C, 9500 g). The supernatant was immediately collected and transferred (1 mL) into a tube. Subsequently, 3 mL of DPPH was added, and the resultant solution's absorbance was determined at a wavelength of 515 nm. A calibration curve was constructed using gallic acid; results were expressed as gallic acid equivalents (%) and reported as mean  $\pm$  SE with 95% confidence intervals.

### Statistical Analysis:

The Shapiro–Wilk test was used to assess the normality of the experimental data, and homogeneity of variances was evaluated before parametric comparisons. Mean, standard error (SE), and 95% confidence interval (CI) were calculated for each experimental group. One-way ANOVA followed by Tukey's post hoc test was used for multiple-group comparisons when assumptions for parametric analysis were satisfied. When distributional assumptions were not met, non-parametric analysis using the Kruskal–Wallis test with appropriate post hoc comparisons was considered. A two-sided p-value <0.05 was considered statistically significant.

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

### Results.

To address reporting clarity, all result figures are labelled with measurement units and present mean  $\pm$  SE with 95% CI, with p < 0.05 used as the threshold for statistical significance (Table 2).

### Changes in arterial pressure:

Chronic administration of L-NAME resulted in a progressive and significant increase in both SAP and DAP in rats, indicating the development of hypertension associated with nitric oxide synthase inhibition.

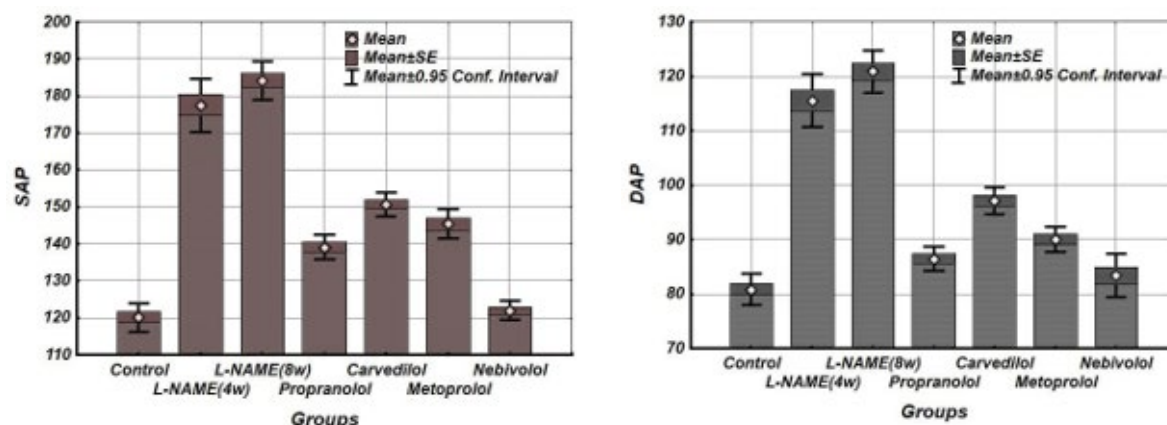
After 4 weeks of L-NAME treatment, both SAP and DAP demonstrated significant increases compared to control animals, with further elevation observed at 8 weeks, highlighting a time-dependent hypertensive effect.

**Table 1.** Experimental groups and treatment protocols.

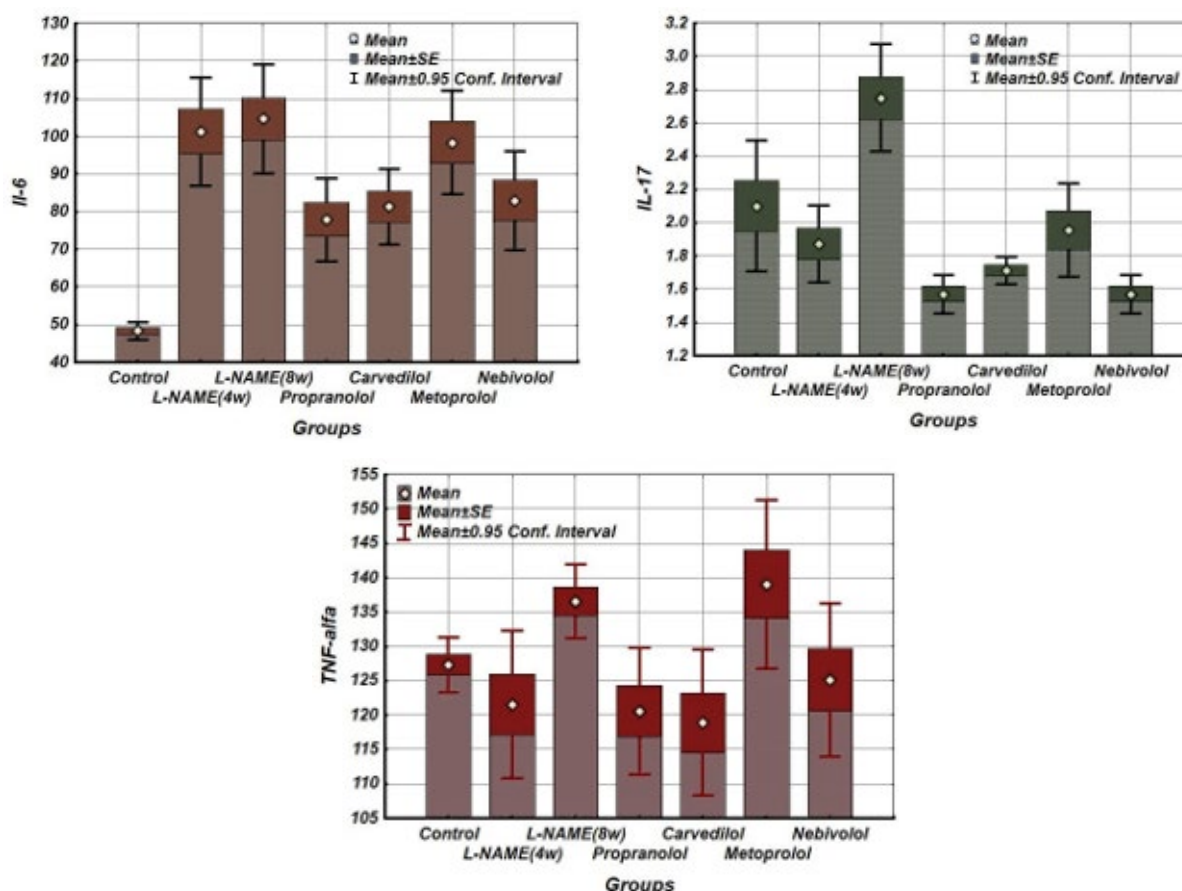
| Group name                              | Treatment protocol                                                                     | N  |
|-----------------------------------------|----------------------------------------------------------------------------------------|----|
| Control-intact (I)                      | Without treatment                                                                      | 10 |
| Hypertension rats (II)                  | Daily L-NAME for 4 weeks (40 mg/kg)                                                    | 10 |
| Hypertension rats (III)                 | Daily L-NAME (daily dose 40 mg/kg) for 8 weeks                                         | 10 |
| Treatment of hypertension in rats (IV)  | Daily L-NAME (40 mg/kg/day) for 8 weeks + nebivolol (0.5 mg/kg/day) during weeks 5–8   | 10 |
| Treatment of hypertension in rats (V)   | Daily L-NAME (40 mg/kg/day) for 8 weeks + propranolol (0.1 mg/kg/day) during weeks 5–8 | 10 |
| Treatment of hypertension in rats (VI)  | Daily L-NAME (40 mg/kg/day) for 8 weeks + metoprolol (3 mg/kg/day) during weeks 5–8    | 10 |
| Treatment of hypertension in rats (VII) | Daily L-NAME (40 mg/kg/day) for 8 weeks + carvedilol (2 mg/kg/day) during weeks 5–8    | 10 |

**Table 2.** Outcome measures, units, laboratory/measurement methods, and presentation format.

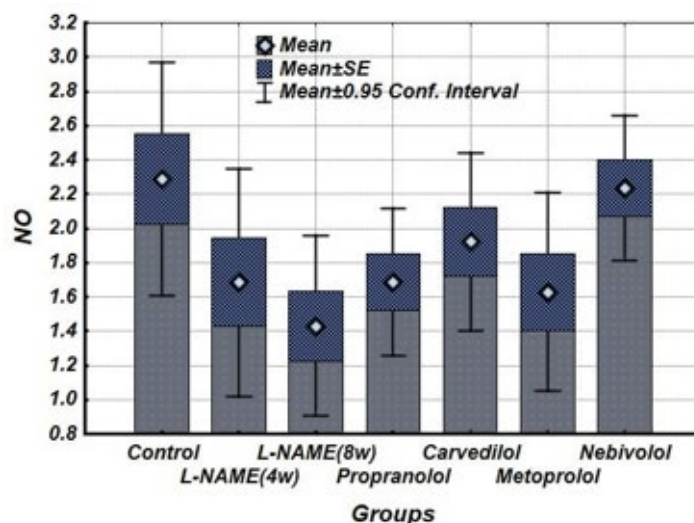
| Outcome measure            | Unit                      | Method                    | Presentation in Results             |
|----------------------------|---------------------------|---------------------------|-------------------------------------|
| SAP and DAP                | mmHg                      | Tail-cuff plethysmography | Figure 1; mean $\pm$ SE with 95% CI |
| IL-6, IL-17, TNF- $\alpha$ | pg/mL                     | Rat ELISA kits            | Figure 2; mean $\pm$ SE with 95% CI |
| NOx metabolites            | mM                        | Modified Griess method    | Figure 3; mean $\pm$ SE with 95% CI |
| TAA                        | % gallic acid equivalents | DPPH-scavenging assay     | Figure 4; mean $\pm$ SE with 95% CI |



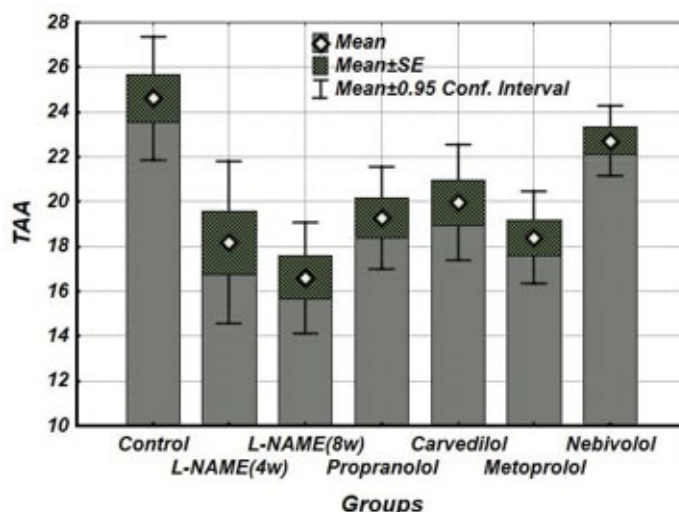
**Figure 1.** Changes in SAP and DAP in L-NAME-treated rats (4 and 8 weeks) and after  $\beta$ -blocker treatment (propranolol, carvedilol, metoprolol, nebivolol). SAP and DAP are expressed in mmHg. Data are presented as mean  $\pm$  standard error (SE) with 95% confidence interval (CI),  $n=10$  per group. Differences between groups were assessed by one-way ANOVA followed by Tukey's post hoc test;  $p < 0.05$  was considered statistically significant.



**Figure 2.** Changes in serum IL-6, IL-17, and TNF- $\alpha$  levels in L-NAME-treated rats (4 and 8 weeks) and after  $\beta$ -blocker treatment. Cytokine concentrations are expressed in pg/mL. Data are presented as mean  $\pm$  SE with 95% CI,  $n=10$  per group. Differences between groups were assessed by one-way ANOVA followed by Tukey's post hoc test;  $p < 0.05$  was considered statistically significant.



**Figure 3.** Changes in blood NOx levels in L-NAME-treated rats (4 and 8 weeks) and after  $\beta$ -blocker treatment. NOx values are expressed in mM. Data are presented as mean  $\pm$ SE with 95% CI,  $n=10$  per group. Differences between groups were assessed by one-way ANOVA followed by Tukey's post hoc test;  $p < 0.05$  was considered statistically significant.



**Figure 4.** Changes in total antioxidant activity (TAA) of the non-enzymatic antioxidant system in L-NAME-treated rats (4 and 8 weeks) and after  $\beta$ -blocker treatment. TAA values are expressed as gallic acid equivalents (%). Data are presented as mean  $\pm$ SE with 95% CI,  $n=10$  per group. Differences between groups were assessed by one-way ANOVA followed by Tukey's post hoc test;  $p < 0.05$  was considered statistically significant.

Subsequent treatment with  $\beta$ -blockers yielded differential effects on these parameters. Propranolol resulted in a moderate reduction in arterial pressure, while carvedilol and metoprolol resulted in a more pronounced decrease in both SAP and DAP. Among all the  $\beta$ -blockers tested, nebivolol exhibited the greatest antihypertensive effect, effectively restoring pressure levels to values comparable to those observed in the control group.

#### Changes in Interleukin Levels:

Chronic inhibition of nitric oxide synthase using L-NAME resulted in a pronounced pro-inflammatory response in rats, characterised by significant elevations in serum interleukin levels (IL-6, IL-17, and TNF- $\alpha$ ).

Following four weeks of L-NAME treatment, IL-6 levels increased significantly and remained elevated after eight weeks. TNF- $\alpha$  and IL-17 levels showed moderate increases, with IL-17 reaching peak levels at eight weeks.

These findings indicate activation of inflammatory pathways associated with nitric oxide deficiency.

Treatment with  $\beta$ -blockers demonstrated varying effects on interleukin levels. Propranolol and carvedilol resulted in modest reductions in IL-6 and TNF- $\alpha$  levels, while metoprolol showed minimal effects. In contrast, nebivolol significantly reduced IL-6, IL-17, and TNF- $\alpha$  levels compared to the L-NAME (8-week) group. However, direct comparative interpretation should be made with caution because equipotent antihypertensive dosing was not established.

#### Changes in NOx levels:

After four weeks of L-NAME treatment, nitric oxide metabolites (NOx) levels decreased from  $2.31 \pm 0.3$  mM in the control group to  $1.62 \pm 0.3$  mM, representing an approximate 30% reduction. After eight weeks, NOx levels further decreased to  $1.3 \pm 0.3$  mM (approximately 44% reduction), indicating sustained inhibition of NO synthesis.

Treatment with  $\beta$ -blockers showed differential effects. Propranolol and metoprolol resulted in modest increases in NOx levels ( $\sim 10\%$  compared to the L-NAME 8-week group). Carvedilol demonstrated a more pronounced increase ( $\sim 40\%$ ), while nebivolol produced the greatest effect, restoring NO levels to  $2.21 \pm 0.3$  mM ( $\sim 70\%$  increase), approaching control values. However, direct comparative interpretation should be made with caution because equipotent antihypertensive dosing was not established.

#### Changes in TAA:

After four weeks of L-NAME treatment, TAA decreased significantly from  $25.32 \pm 0.36\%$  in the control group to  $18.5 \pm 0.32\%$  (approximately 27% reduction). After eight weeks, TAA decreased further to  $16.2 \pm 0.35\%$ .

Treatment with  $\beta$ -blockers resulted in varying degrees of recovery. Propranolol and metoprolol produced modest increases ( $\sim 10\%$ ), while carvedilol showed a greater improvement ( $\sim 12\%$ ). The most pronounced effect was observed with nebivolol, which increased TAA to  $22.6 \pm 0.33\%$ , approaching control values.

These results indicate that  $\beta$ -blockers, particularly nebivolol, were associated with improved antioxidant status under conditions of nitric oxide deficiency. However, direct comparative interpretation should be made with caution because equipotent antihypertensive dosing was not established.

#### Discussion.

This study shows that chronic inhibition of nitric oxide synthase (NOS) using L-NAME induces hypertension accompanied by alterations in interleukin levels, nitric oxide (NO) metabolites, and TAA.

Consistent with previous studies, L-NAME administration resulted in a progressive increase in arterial pressure, confirming the establishment of an experimental hypertensive state [4,15]. Importantly, the elevation in blood pressure observed in this study is best interpreted as a hemodynamic consequence of NOS inhibition rather than direct evidence of impaired endothelial function, as endothelial function was not directly assessed. Similar observations have been reported in experimental models in which NO deficiency increases vascular tone and peripheral resistance [10,11,15].

The observed decrease in circulating NO metabolites supports effective inhibition of NOS and reduced NOx concentrations and decreased NO bioavailability. However, because the present study evaluates systemic NO metabolites, these findings do not allow direct conclusions regarding endothelial function at the vascular level.

Hypertension is increasingly recognised as a multifactorial condition involving immune activation, oxidative stress, and vascular dysfunction, in addition to hemodynamic alterations [25-27]. In this context, the observed increase in circulating interleukins (IL-6, IL-17, and TNF- $\alpha$ ) is consistent with previous evidence demonstrating activation of inflammatory pathways in hypertension [8,13]. These cytokines are known to contribute to vascular dysfunction through mechanisms including oxidative stress, immune cell activation, and modulation of vascular signalling pathways [12-14,28-30].

The concomitant reduction in TAA further indicates the presence of oxidative imbalance. TAA reflects the overall capacity of circulating antioxidants but does not provide information on specific enzymatic defence systems. These findings are consistent with established evidence linking oxidative stress to reduced NO bioavailability and vascular dysfunction [25,31,32].

Importantly, although parallel changes in NO metabolites, interleukin levels, and antioxidant capacity were observed, the present study design does not allow causal relationships to be established. Previous studies suggest a bidirectional interaction, in which reduced NO availability may promote inflammatory activation, while inflammatory mediators may further impair NO signalling [10,11,25,31]. Thus, the present findings should be interpreted as reflecting interconnected but not causally defined processes.

Regarding pharmacological interventions,  $\beta$ -blockers exhibited differential effects on both hemodynamic and biochemical parameters. Nebivolol and carvedilol produced more pronounced improvements compared with propranolol and metoprolol. These differences are consistent with their additional pharmacological properties, including vasodilatory and antioxidant effects [20,21,33,34]. Nebivolol has been reported to enhance NO bioavailability via  $\beta_3$ -adrenergic receptor-mediated mechanisms [33,34], whereas carvedilol exerts antioxidant and anti-inflammatory effects, including inhibition of NLRP3 inflammasome activation [21]. These properties may partially explain their greater efficacy; however, mechanistic confirmation was beyond the scope of this study. In addition, the  $\beta$ -blockers were administered at pharmacologically relevant but non-equivalent doses; therefore, differences between agents should be interpreted cautiously and cannot be considered evidence of superior efficacy.

From a translational perspective, these findings suggest that antihypertensive agents with additional anti-inflammatory and antioxidant properties may provide broader benefits beyond blood pressure reduction alone, particularly in conditions characterised by immune activation and oxidative stress. However, extrapolation to clinical settings should be made cautiously, as the present study was conducted in an experimental model and does not account for the complexity of human hypertension.

The L-NAME model is particularly useful for examining NO-deficiency-related hypertension, oxidative imbalance, and inflammatory activation; therefore, it is appropriate for the mechanistic aims of this study. Nevertheless, human essential hypertension is heterogeneous and involves renal, neurohumoral, metabolic, genetic, environmental, and age-related factors that are not fully reproduced by pharmacological NOS inhibition. Consequently, the present findings should be viewed as hypothesis-generating and should not be interpreted as direct clinical proof of comparative  $\beta$ -blocker superiority.

Overall, the present results are consistent with the concept that hypertension involves interconnected hemodynamic, inflammatory, and oxidative mechanisms. However, the study identifies associations among these factors rather than direct mechanistic pathways; therefore, interpretation should remain conservative and hypothesis-generating.

## Limitations.

This study has several limitations. First, the experimental design allows identification of associations between nitric oxide metabolites, cytokine levels, and oxidative status but does not establish causal relationships. Second, measurements were limited to systemic biomarkers and did not include direct assessment of endothelial function, vascular reactivity, tissue cytokine expression, vascular histology, or specific antioxidant enzyme activities. Third, the L-NAME model reflects NO-deficiency-driven hypertension and does not fully reproduce the multifactorial nature of human essential hypertension. Fourth, only male rats were used, which limits the assessment of sex-related differences. Fifth, tail-cuff plethysmography is non-invasive and suitable for repeated measurements, but it may be influenced by restraint and thermal stress despite acclimatisation. Therefore, translation of these findings to clinical hypertension should be cautious.

An additional limitation of the present study relates to the comparison of  $\beta$ -blockers. The investigated agents were administered at different doses selected from previously published experimental studies and based on their distinct pharmacokinetic and pharmacodynamic characteristics. Consequently, the treatment regimens were not designed to achieve equipotent antihypertensive effects. Therefore, differences observed between  $\beta$ -blockers should be interpreted cautiously and should not be considered definitive evidence of superior efficacy of any individual agent. Future studies employing dose-equivalent protocols and pharmacodynamic normalisation are required to enable more rigorous comparative evaluation of  $\beta$ -blocker effects on inflammatory and oxidative pathways in hypertension.

## Conclusion.

In conclusion, chronic inhibition of nitric oxide synthase using L-NAME induces hypertension in rats and is associated with reduced nitric oxide metabolites, increased pro-inflammatory interleukins, and decreased total antioxidant activity.

The present findings demonstrate associations between hemodynamic, inflammatory, and oxidative changes rather than direct mechanistic relationships.

$\beta$ -blocker treatment attenuated hypertension and partially restored inflammatory and oxidative stress parameters, with nebivolol and carvedilol demonstrating the most pronounced effects under the conditions of this experimental model. These differences may reflect their additional pharmacological properties, including vasodilatory and antioxidant actions.

From a translational perspective, these results suggest that antihypertensive agents targeting not only blood pressure but also inflammatory and oxidative pathways may provide broader therapeutic benefits. Because the findings were obtained in an L-NAME-induced animal model and  $\beta$ -blockers were not compared using dose-normalised protocols, clinical extrapolation should be approached with caution. Further mechanistic and translational studies are required.

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