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# Interleukin-Driven Inflammation in L-NAME-Induced Hypertension: Comparative Effects of β-Blockers on Endothelial Function

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## ABSTRACT

Background: Hypertension is a multifactorial disorder involving endothelial dysfunction, oxidative stress, and chronic low-grade inflammation. Interleukin (IL)-mediated pathways play a crucial role in the pathogenesis of vascular inflammation, while nitric oxide (NO) deficiency and oxidative imbalance further sustain elevated arterial pressure. Beta-adrenergic blockers (β-blockers) are effective antihypertensive agents; however, their anti-inflammatory and antioxidant effects vary with their pharmacodynamic profiles.

Objectives: The study aims to assess the role of interleukin-mediated inflammation in hypertension induced by nitric oxide synthase (NOS) inhibition, and to compare the antihypertensive, antioxidant, and anti-inflammatory effects of different β-blockers (propranolol, metoprolol, carvedilol, nebivolol).

Methods: In 86 male rats, hypertension was induced by intraperitoneal administration of L-NAME (40 mg/kg). After 4 weeks of L-NAME treatment, animals received one of four β-blockers (Nebivolol 0.5 mg/kg, propranolol 0.1 mg/kg, metoprolol 3 mg/kg, or carvedilol 2 mg/kg) for the subsequent 4 weeks. Systolic and diastolic arterial pressure (SAP, DAP) were measured non-invasively. ELISA was used to determine serum interleukin levels (IL-6, IL-17, TNF-α).

Results: Chronic L-NAME administration resulted in progressive hypertension accompanied by a significant increase in IL-6, IL-17, and TNF-α. β-blocker treatment attenuated these changes to varying extents. Propranolol and metoprolol produced only modest reductions in blood pressure and cytokine levels. Carvedilol significantly lowered IL-6, IL-17, and TNF-α. Nebivolol exerted the most potent effect: arterial pressure returned to near control levels, and cytokine levels (IL-6, IL-17, TNF-α) approached control levels.

Conclusions: The interplay between interleukin-mediated inflammation and chronic NOS inhibition maintains hypertension. β-blockers with vasodilatory and antioxidant properties (particularly nebivolol and carvedilol) restore endothelial function more effectively and suppress inflammation more than classical β-blockers. Targeting the oxidative–inflammatory axis may improve outcomes in hypertension associated with inflammation.

Keywords: β-blockers; carvedilol; hypertension; interleukins; nebivolol, Nω-nitro-L-arginine methyl ester (L-NAME).

## BACKGROUND

Hypertension is a complex cardiovascular disorder and a major contributor to morbidity and mortality worldwide.[1,2] Its pathogenesis involves genetic predisposition, neurohumoral dysregulation, endothelial dysfunction, oxidative stress, and chronic low-grade inflammation.[3-6] The heterogeneity of these mechanisms contributes to variable therapy responses among patients.

In recent years, increasing evidence has highlighted the immune system's involvement in hypertension.[7-9] Pro-inflammatory cytokines - including interleukins (ILs) such as IL-6, IL-17, and tumour necrosis factor α (TNF-α) - play central roles in vascular dysfunction, remodelling, and sustained high blood pressure.[10] These cytokines have been found elevated in hypertensive patients and in experimental animal models (e.g., angiotensin-II–induced or spontaneous hypertension).

The model of hypertension induced by chronic administration of Nω-nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase (NOS) inhibitor, is widely used to mimic key features of essential hypertension - NO deficiency, endothelial dysfunction, increased oxidative stress, and vascular inflammation.[11]

β-adrenergic blockers (β-blockers) are well-established antihypertensive agents. Beyond their classical hemodynamic effects, several β-blockers exhibit antioxidant and anti-inflammatory properties.[12-14] Their efficacy in modulating immune and oxidative parameters varies significantly depending on their pharmacological profile (receptor selectivity, vasodilatory action, antioxidant capacity). Notably, newer agents such as carvedilol and nebivolol may provide vascular protection beyond blood pressure lowering.[15,16]

In this study, we aimed to (i) elucidate the role of interleukin-mediated inflammatory pathways in L-NAME-induced hypertension, and (ii) compare the effects of four β-blockers (propranolol, metoprolol, carvedilol, nebivolol) on cytokine balance and arterial pressure.

## METHODS

### Animals and experimental design

Eighty-six white male rats were housed under standard laboratory conditions (controlled temperature, 12-hour light/dark cycle, free access to food and water). Hypertension


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was induced by intraperitoneal administration of L-NAME (Sigma-Aldrich) at 40 mg/kg daily. All procedures were approved by the Animal Ethics Committee at Tbilisi State Medical University (Protocol, Date: 26 July 2022).

Rats were randomly allocated into seven groups: Group 1 - Control (intact) (no treatment); Group 2 - Hypertension 4 weeks: L-NAME 40 mg/kg daily for 4 weeks; Group 3 - Hypertension 8 weeks: L-NAME 40 mg/kg daily for 8 weeks; Group 4 - L-NAME + nebivolol: L-NAME 40 mg/kg daily for 4 weeks, then nebivolol 0.5 mg/kg daily for 4 weeks; Group 5 - L-NAME + propranolol: L-NAME 40 mg/kg daily for 4 weeks, then propranolol 0.1 mg/kg daily for 4 weeks; Group 6 - L-NAME + metoprolol: L-NAME 40 mg/kg daily for 4 weeks, then metoprolol 3 mg/kg daily for 4 weeks; Group 7 - L-NAME + carvedilol: L-NAME 40 mg/kg daily for 4 weeks, then carvedilol 2 mg/kg daily for 4 weeks.

### Blood pressure measurement

Systolic (SAP) and diastolic arterial pressures (DAP) were measured daily by non-invasive tail-cuff plethysmography using PhysioSuite (Kent Scientific, Russia).

### Immunological analyses

At the end of the 4th and 8th weeks, animals were euthanised under anesthesia, and aortic blood samples were collected. Serum was separated and stored.

Interleukins: serum IL-6, IL-17, and TNF-α concentrations were measured using commercial Rat ELISA Kits (Fine Test) on the HUMAN HS platform, following the manufacturer's instructions.

### Statistical analysis

The Shapiro-Wilk test was used to assess the normality of the experimental data. Mean, Standard Error, and 95% 95 confidence intervals were calculated for each experimental group. Analysis of Variance (Factorial ANOVA) was used to analyse differences in the mean values across the different experimental groups.

Statistical software SPSS-11 was used for data analysis and visualisation of results.

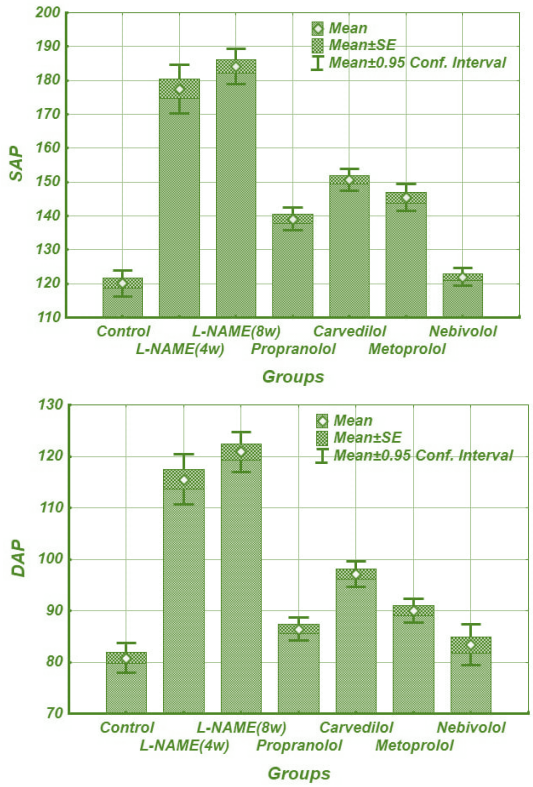
## RESULTS

### Blood pressure

Chronic L-NAME administration caused a progressive increase in both systolic and diastolic arterial pressure, confirming the development of sustained hypertension. Compared with control rats, SAP and DAP were significantly elevated after 4 weeks of L-NAME treatment, with further increases at 8 weeks (Fig.1).

In β-blocker–treated groups, reductions in SAP and DAP varied: propranolol produced modest lowering; metoprolol showed a somewhat greater effect; carvedilol led to more pronounced pressure reductions; and nebivolol normalized SAP and DAP nearly to control values. (Fig.1).

FIGURE 1. Alterations of SAP and DAP in L-NAME administered rats (during 4-8 weeks) and after the last 4 weeks with β-blockers (propranolol, carvedilol, metoprolol, and nebivolol) treatment




Abbreviations: DAP, diastolic blood pressure; L-NAME, Nω-nitro-L-arginine methyl ester; SAP, systolic blood pressure.

### Interleukin profile

L-NAME–induced NOS inhibition triggered a marked pro-inflammatory response. Serum IL-6 was significantly elevated after 4 weeks and remained high at 8 weeks. IL-17 and TNF-α levels increased progressively, reaching their highest levels after 8 weeks.

### Upon β-blocker therapy

Propranolol and metoprolol achieved only small reductions in IL-6 and TNF-α; IL-17 remained elevated.

Carvedilol significantly reduced IL-6, IL-17, and TNF-α compared to the 8-week L-NAME group.

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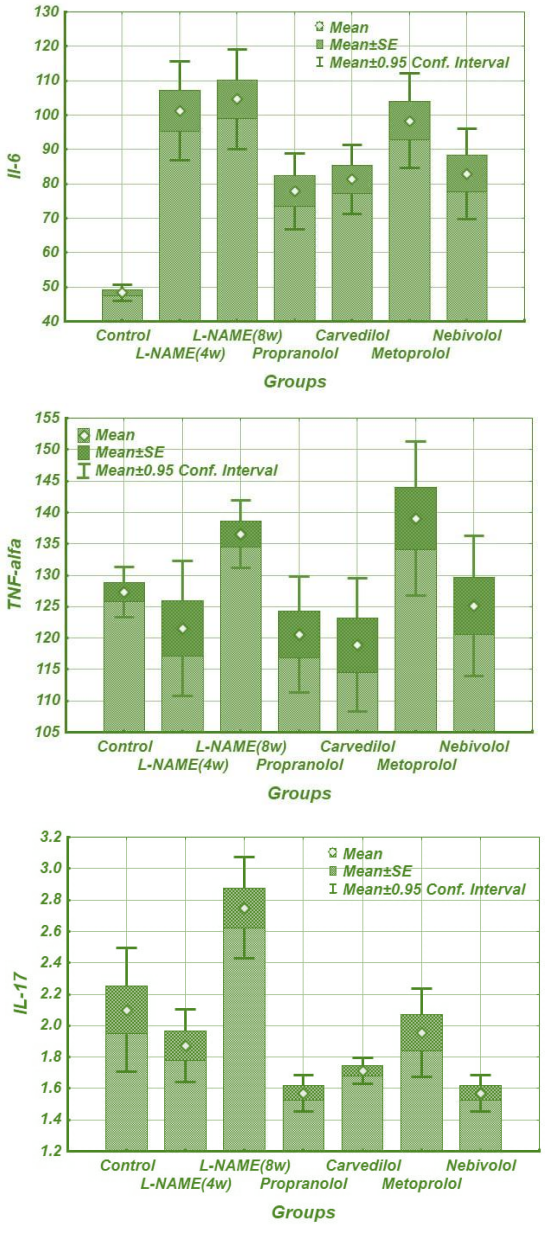
Nebivolol produced the most significant suppression of all three cytokines, bringing their levels close to those of control animals (Fig.2).

TABLE 2. Alterations of blood IL-6, IL-17, and TNF-α content in L-NAME administered rats (during 4-8 weeks) and after the last 4 weeks β-blockers (propranolol, carvedilol, metoprolol, and nebivolol) treatment




Abbreviations: IL-6, interleukin 6; IL-17, interleukin 17; L-NAME, Nω-nitro-L-arginine methyl ester; TNF-alfa, tumor necrosis factor-alfa.

## DISUCSSION

This study demonstrates that chronic inhibition of NOS via L-NAME produces sustained hypertension and systemic inflammation, supporting the notion that impaired NO signaling is central to hypertensive pathogenesis. Elevated serum IL-6, IL-17, and TNF-α confirm activation of interleukin-mediated inflammatory pathways.[17]

The interplay between NO depletion and inflammation forms a pathological feedback loop. A similar inflammatory amplification has been described in T-cell- and cytokine-driven models of hypertension.[18]

Among the β-blockers tested, nebivolol and carvedilol, which possess vasodilatory and antioxidant properties, showed a superior capacity to restore endothelial function and suppress inflammation compared to classical β-blockers (propranolol, metoprolol).[19] Nebivolol exhibited the most potent effects, likely due to its ability to stimulate endothelium-dependent NO release (via $\beta_3$-adrenergic mechanisms). Carvedilol also provided significant benefits, consistent with its dual $\beta/\alpha_1$-blocking.[20]

These results support the concept that hypertension is not only a hemodynamic disorder but also a neuroimmune-vascular disease. Therefore, antihypertensive strategies should aim beyond blood-pressure reduction and include modulation of oxidative and inflammatory pathways - particularly in patients with elevated inflammatory markers or evidence of endothelial dysfunction.

## CONCLUSIONS

In an L-NAME–induced model of NO-deficient hypertension, NO depletion and interleukin-mediated inflammation drive sustained high blood pressure. β-blockers with vasodilatory and antioxidant properties - especially nebivolol and carvedilol - more effectively restore NO bioavailability, and suppress pro-inflammatory cytokines than conventional β-blockers. Targeting the inflammatory axis may enhance therapeutic efficacy in hypertension associated with vascular inflammation and endothelial dysfunction.

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