

G.M. Imamaliyev, A.A. Nuriyev, Kh.I. Gurbanova, L.G. Amrahova, I.Ch. Alikhanova,
S.A. Bayramova, S.A. Aliyeva
Azerbaijan Medical University, Baku, Azerbaijan

MODULATING EFFECT OF CARVEDILOL ON ACTIVATION OF CYTOKINES IN PATIENTS WITH CHRONIC HEART FAILURE CAUSED BY ARTERIAL HYPERTENSION

e-mail: geyrat@mail.ru

To assess the 6-month treatment with carvedilol, depending on the levels of proinflammatory cytokines (interleukin-1, interleukin-6 and tumor necrosis factor- α) in patients with arterial hypertension associated with chronic heart failure. The observation and treatment were conducted in 43 patients (mean age 51.3 \pm 3.2 years). The patients were divided in two groups. In patients of the 1st group with chronic heart failure of the II class according to New York Heart Association (n=22), the blood content of proinflammatory cytokines (p<0.05) reduced after treatment. In patients of the 2nd group with chronic heart failure of the III class according to New York Heart Association (n=21), the levels of cytokines also reduced after treatment (p<0.05). The change of cytokine level correlates with the improvement of global function of the left ventricle and arterial pressure. Thus, carvedilol is highly effective for correction of the activation of cytokines in patients with chronic heart failure caused by arterial hypertension.

Key words: chronic heart failure, proinflammatory cytokines, interleukin-1, interleukin-6, tumor necrosis factor-alpha.

Г.М. Імамалієв, А.А. Нурієв, Х.І. Гурбанова, Л.Г. Амрахова, І.Ч. Аліханова,
С.А. Байрамова, С.А. Алієва

МОДУЮЩИЙ ВПЛИВ КАРВЕДИЛОЛУ НА АКТИВІЗАЦІЮ ЦИТОКІНІВ У ПАЦІЄНТІВ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ НА ФОНІ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ

Метою дослідження є оцінка впливу 6-місячної терапії карведилолом на рівень прозапальних цитокінів (інтерлейкіну-1, інтерлейкіну-6 та фактору некрозу пухлини- α) у хворих на артеріальну гіпертензію у поєднанні з хронічною серцевою недостатністю. Під наглядом та лікуванням перебували 43 пацієнти (середній вік 51,3 \pm 3,2 роки). Пацієнти були поділені на дві групи. У пацієнтів 1-ї групи з хронічною серцевою недостатністю II класу за класифікацією Нью-Йоркської кардіологічної асоціації (n=22) після лікування знизився вміст прозапальних цитокінів у крові (p<0,05). У пацієнтів 2-ї групи з хронічною серцевою недостатністю III класу за класифікацією Нью-Йоркської кардіологічної асоціації (n=21) після лікування також знизився рівень цитокінів (p<0,05). Зміна рівня цитокінів корелює з покращенням глобальної функції лівого шлуночка та артеріального тиску. Таким чином, карведилол є високоефективним для корекції активації цитокінів у хворих на хронічну серцеву недостатність, зумовлену артеріальною гіпертензією.

Ключові слова: хронічна серцева недостатність, прозапальні цитокіни, інтерлейкін-1, інтерлейкін-6, фактор некрозу пухлин альфа.

Currently, it is advisable to consider the pathogenesis of chronic heart failure (CHF) in the light of modern concepts in the field of cardiology, endocrinology, immunology and molecular medicine. One of the latest achievements of modern cardiology is the establishment of the role of activation of the cytokine system in the pathogenesis of CHF [1–3].

This mechanism is based on the idea of non-specific activation of macrophages and monocytes in the interstitial fluid as an inducer of the synthesis of pro-inflammatory cytokines that determine the evolution of dysfunction of the left ventricle (LV) of the heart. In patients with arterial hypertension, the production of cytokines is caused by the activation of the sympathetic-adrenal system, increased catabolism and the development of an immunosuppressive effect due to hypoxia [5, 7]. Despite the reliability of hyperactivation of the neurohumoral system in the pathogenesis of CHF, many clinical indicators have recently appeared, the influence of which is very difficult to explain. Cytokines in normal and pathological conditions carry out intercellular communication as messengers. They create communication networks of the immune system at the tissue and organ level. Therefore, when the synthesis and expression of the cytokine system is disrupted, intercellular communication is disrupted, and eventually a pathological process develops [4, 12].

Cytokines are produced along with inflammatory cells in cardiomyocytes and endothelial cells. In CHF, cytokines reduce the ability of the myocardium to contract, have a damaging effect on the myocardium, accelerate apoptosis, increase the induction of nitric oxide (NO), increase the density of angiotensin II (ATII) receptors on the endothelial surface, and finally cause cardiac cachexia. It was found that tumor necrosis factor α (TNF α) in patients with CHF increases even more when compared with healthy people. This has been proven in publications in recent years, so that the level of TNF α in CHF directly correlates with the severity of heart failure [9–11].

Activation of the systolic arterial pressure in patients with arterial hypertension against the background of CHF is the main trigger for cytokine activation [4]. Therefore, the existing close relationship between the activation of the SAS and the inflammatory cytokine response is a direct indication for the use of β -blockers in this group of patients. At the same time, the influence of a number of new generation's β -blockers and the α -adrenergic blocker carvedilol on this system has not been fully studied [8].

Interleukin-1 (IL-1) has a proinflammatory effect and in CHF has a depressive effect on myocardial contraction by suppressing the contractility of the heart, promoting the progression of myocardial hypertrophy and causing apoptosis of cardiomyocytes. This effect synergizes with the effect of $\text{TNF}\alpha$. The role of IL-1 in apoptosis, hypertrophy and arrhythmogenesis has been proven. An increase in IL-6 in plasma leads to symptomatic or asymptomatic dysfunction of the left ventricle [7, 8]. Among the many effects of IL-6, its role in systemic inflammation as the main acute phase mediator, stimulating the production of acute phase proteins by hepatocytes, should be noted. Increased IL-6 levels significantly correlate with ventricular dysfunction and activation of the neurohumoral system [6].

The key mechanisms for the implementation of the hemodynamic and clinical influence of cytokines in CHF can be grouped as follows:

- 1) negative inotropic effect;
- 2) cardiac remodeling (irreversible dilation of cavities and hypertrophy of cardiomyocytes (CMC);
- 3) disturbances of endothelium-dependent dilation of arterioles;
- 4) increased apoptosis of cardiomyocytes and peripheral muscle cells [5].

Activation of the immune system in patients with CHF plays an important role and requires special treatment. Proinflammatory cytokines $\text{TNF}\alpha$, IL-1, IL-6 actively participate in this process and have a significant impact on the evolution of CHF.

Thus, a relationship between the biosynthesis of IL-6 and $\text{TNF}\alpha$ was established and that the concentration of IL-6 in blood plasma is a more accurate predictor of survival [12].

The purpose of the study was to assess the activity of the cytokine system in patients with chronic heart failure against the background of arterial hypertension and its modulation and regression of hemodynamic parameters during a 6-month course of therapy with carvedilol.

Materials and methods. The study was conducted at the Azerbaijan Medical University in the period from 2022 to 2023.

The study involved patients with CHF against the background of arterial hypertension, whose average age was 51.3 ± 3.2 years. The diagnosis of chronic heart failure was confirmed according to the classification of the New York Heart Association (NYHA).

Inclusion criteria: CHF II–III functional class (FC), arterial hypertension

Exclusion criteria: CHF I functional class, normal blood pressure

The patients were diagnosed with CHF II–III functional class according to the classification of the New York Heart Association (NYHA). A total of 43 patients (29 men and 14 women) were examined. The patients were divided into 2 groups. Group 1 (NYHA FC II) included 22 patients, and Group 2 (NYHA FC III) included 21 patients. The patients took carvedilol (Carvedilol Sandoz®, Slovenia) at a dose of 12.5–25 mg once a day for 6 months. The control group consisted of 28 practically healthy individuals (20 men and 8 women). Their average age was 42.4 ± 5.6 years.

In the studied patients, cytokines IL-1, IL-6 and $\text{TNF}\alpha$ were determined in the blood serum using the CYTELISA test system and enzyme-linked immunosorbent assay according to a standard method.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were studied in patients. Using echocardiography (Vivid 4 US, “General Electric”, USA), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), ejection fraction (EF%), and left ventricular mass index (LVMI) were determined. Statistical data processing was performed using the Statistica 6.0 for Windows program. Standard statistical methods were used, in particular, the calculation of the unpaired Student's t-test to assess the reliability of differences between groups. The data are presented as $M \pm m$, where M is the mean value, m is the standard error of the mean. The significance level was considered reliable at $p < 0.05$, $p < 0.01$.

Results of the study and their discussion. When comparing, group I patients with the control group, the content of IL-1 ($p < 0.05$), IL-6 ($p < 0.05$), $\text{TNF}\alpha$ ($p < 0.05$) significantly increased. The data in Table 1 indicate that during decompensation of CHF, the levels of systemic inflammation markers increase significantly, and all parts of the immune system are activated; statistically significant differences were noted when comparing between groups. The same data were obtained in the II group of patients when compared with the control IL-1 ($p < 0.01$), IL-6 ($p < 0.01$), $\text{TNF}\alpha$ ($p < 0.01$) (Table 1).

Table 1

Effect of carvedilol on cytokine indices in patients with CHF developing against the background of arterial hypertension

Indicators	Control Group	Group I		Group II	
		Before treatment	After treatment	Before treatment	After treatment
IL-1, pq/ml	32.9±1.3	39.1±2.5*	33.2±2.1#	58.2±3.3**	46.1±3.2##
IL-6, pq/ml	30.1±2.1	36.2±2.2*	31.3±2.3#	56.1±2.5**	43.1±3.4##
TNFα, pq/ml	9.8±1.2	16.3±2.4*	11.2±1.5#	19.6±3.2**	12.2±2.5#

Notes: * p<0.05; ** p<0.01; when comparing with the reliability control, # p<0.05; ## p<0.01 when comparing before and after treatment indicators.

The results showed an increase in the activity of the cytokine system depending on the FC. When comparing the data obtained after 6 months of treatment with the data at the beginning of treatment in the I group (IL-1 (p<0.05), IL-6 (p<0.05), TNFα (p<0.05)) and in the II group also (IL-1 (p<0.01), IL-6 (p<0.01), TNFα (p<0.05)) the values significantly decreased.

Correction of the cytokine system improved hemodynamic parameters. Thus, SBP after the treatment in patients significantly decreased in both groups (p<0.01). Thus, the value of SBP in I group was 141.1±6.2 mmHg, after treatment it decreased till 122.2±5.3 mmHg. In the II group the patients demonstrated the similar results (142.4±7.8 mmHg and 123.1±4.2 mmHg, respectively).

Comparison of DBP also revealed the positive effect in both groups. The value of DBP in I group before treatment was at the level of 91.2±2.3 mmHg, after treatment it was lower and showed the average level of 82.2±4.2 mmHg, which was significantly differ. The similar results were obtained related to II group.

When comparing the data on LVEDV and LVESD at the beginning of treatment and after, a significant decrease in these parameters was revealed in both groups (p<0.01). Thus, the levels of LVEDV in groups with II FC and III FC before treatment were 166.3±4.8 mm³ and 171.8±3.2 mm³, respectively. After treatment the results demonstrated decreasing till 141.3±4.3 mm³ and 146.9±4.1 mm³, respectively (p<0.01). The changes in LVESD levels were characterized with the same trends, and decreased after treatment in both groups (p<0.01).

The ejection fraction also significantly (p<0.05) increased. In the I group it became higher after treatment compared previous results (46.1±1.2% and 52.5±1.9 %, respectively, meanwhile in the II group the levels of EF before and after therapy were 48.5±1.4 % and 51.1±1.7 %, respectively (Table 2).

Table 2

Effect of carvedilol on hemodynamic parameters of patients with CHF developing against the background of arterial hypertension

Indicators	II FC		III FC	
	Before treatment	After treatment	Before treatment	After treatment
SBP	141.1±6.2	122.2±5.3**	142.4±7.8	123.1±4.2**
DBP	91.2±2.3	82.2±4.2**	92.4±4.2	81.4±3.4**
LVEDV	166.3±4.8	141.3±4.3**	171.8±3.2	146.9±4.1**
LVESV	97.7±4.6	81.9±5.8**	99.6±5.3	79.2±4.6**
EF%	46.1±1.2	52.5±1.9*	48.5±1.4	51.1±1.7*
LVMI q/m ²	123.2±6.5	105.3±7.8*	126.4±7.6	106.1±5.9*

Notes: * p<0.05; ** p<0.01 – after treatment.

A decrease in the mass of the left ventricular myocardium was detected. This is confirmed LVMI data when comparing it at the beginning and at the end of treatment (p<0.05).

Based on the data obtained, it can be noted that the new cytokine theory does not deny the role of the neurohumoral theory. It additionally explains the mechanisms of CHF formation, expands the basis for therapeutic treatment and opens up new prospects for patients with decompensation.

Numerous studies have demonstrated a correlation between the progression of heart failure and elevated concentrations of the pro-inflammatory cytokine TNFα, along with its downstream mediator interleukin-6 (IL-6), highlighting their promise as potential biomarkers. Contemporary research is increasingly centered on elucidating the underlying pathways through which these inflammatory mediators drive myocardial dysfunction and contribute to the pathogenesis of heart failure. Moreover, attention is being directed toward how persistent activation of pro-inflammatory signaling and its interaction with the

sympathetic nervous system can suppress anti-inflammatory mechanisms, thereby exacerbating disease progression [9].

Several studies devoted in problem of genetic predisposition. Hedayat M, et al (2018), studied genetic features of TNF α gene in patients with ischemic heart failure, revealed that the A/A genotype at the -238 position of the TNF α gene was observed significantly more often in individuals with ischemic heart failure compared to the control group ($p=0.043$), whereas the G/A genotype at this locus showed a notable reduction in frequency among patients ($p=0.018$). Among all haplotypes, the A/A variant of TNF α was the most prevalent in the patient cohort, with statistical significance when compared to controls ($p=0.003$). Specific alleles, genotypic variants, and haplotypes within the TNF α gene, but not within IL-6, appear to be disproportionately represented in patients suffering from ischemic heart failure, suggesting a possible genetic predisposition associated with TNF- α polymorphisms. In our work the genetic factors were not assessed, but the results support the theory of cytokine role in cardiovascular diseases [6].

Under hypertensive conditions, the vascular endothelium experiences mechanical stretch, which influences the differentiation pathways of monocytes. Experimental data indicate that when human monocytes are co-cultured with mechanically stretched aortic endothelial cells, there is a marked increase in the mRNA expression of several pro-inflammatory cytokines, such as IL-6, IL-1 β , and TNF α [12].

Loperena R., et al (2018) in their review noted that inhibition of IL-6 signaling and suppression of hydrogen peroxide production were found to prevent the differentiation of intermediate monocytes in response to mechanical stretching of endothelial cells. Angiotensin II has been implicated both in the pathogenesis of hypertension and in promoting IL-6 secretion by human vascular smooth muscle cells. Additionally, catecholamines have been shown to induce IL-6 production in endothelial cells. Experimental IL-6 administration increased epithelial sodium channel (ENaC) expression in murine kidney cortical collecting duct cells. Correspondingly, studies involving IL-6-deficient mice demonstrated that IL-6 plays a critical role in mediating angiotensin II- and salt-induced elevations in blood pressure [8].

Silva, et al (2019) described the role of pro-inflammatory cytokines and emphasized that the three most commonly involved cytokines concerning heart failures are TNF- α , IL-1, and IL-6, which was confirmed in our work. With synergic interactions, they are all capable of amplifying the inflammatory response of preexistent cardiac alterations, especially those that obliterate blood vessels [10].

Various cardiovascular conditions, including coronary artery disease, atherosclerosis, and congestive heart failure, are characterized by elevated concentrations of pro-inflammatory cytokines such as interferon-gamma (IFN- γ), interleukin-1 β (IL-1 β), IL-6, and TNF α . These inflammatory mediators play a pivotal role in the initiation and progression of atherosclerotic lesions. The development of atheromatous plaques – comprising lipid-laden macrophages, mast cells, T-lymphocytes, and other cellular debris – takes place within the tunica intima, the innermost layer of arterial walls, beginning as fatty streaks on the endothelium [2].

Thus, it can be noted that the cytokine system in patients with CHF is a trigger marker that contributes to the progression process and process regression. Involvement of pro-inflammatory cytokines in processes of decreased elasticity and impaired relaxation of the myocardium LV can be of great importance in the development of new drugs agents designed to delay the progression of CHF. Neutralization of proinflammatory cytokines and blockade of intracellular signaling pathways in which they participate are among the most promising therapeutic strategies in the near future. At the same time, the levels of inflammation markers are more dynamic indicators, which was demonstrated in the present study by identifying significant changes in proinflammatory markers by the end of the 6th month of therapy. These data allow us to develop new methods for assessing the effectiveness of CHF treatment not only from the standpoint of normalizing hemodynamic parameters, but also from the point of view of suppressing systemic inflammation and preventing progression.

Conclusions

1. In patients of the 1st group with chronic heart failure of the II class according to New York Heart Association, the blood content of proinflammatory cytokines ($p<0.05$) reduced after treatment. The same changes were detected in patients of the 2nd group with chronic heart failure of the III class according to New York Heart Association.

2. The change of cytokine level correlates with the improvement of global function of the left ventricle and arterial pressure. Thus, carvedilol is highly effective for correction of the activation of cytokines in patients with chronic heart failure caused by arterial hypertension.

The key mechanisms of reducing cytokine levels in patients with CHF during treatment with carvedilol are most likely associated with its anti-ischemic, antioxidant, remodeling properties, as well as with blocking the action of catecholamines on the myocardium. Further study of the role of proinflammatory cytokines in the development and progression of cardiovascular diseases will allow us to finally clarify and detail the mechanisms of their pathogenesis, which in turn will allow us to understand their complex impact on the body as a whole, as well as obtain information for the creation of new effective and safe specific drugs.

References

1. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. *Nat. Rev. Cardiol.* 2020; 17: 269–285. doi: 10.1038/s41569-019-0315-x.
2. Amin MN, Siddiqui SA, Ibrahim M, Hakim ML, Ahammed MS, Kabir A, et al. Inflammatory cytokines in the pathogenesis of cardiovascular disease and cancer. *SAGE Open Med.* 2020 Oct 20;8:2050312120965752. doi: 10.1177/2050312120965752.
3. de Freitas RA, Lima VV, Bomfim GF, Giachini FRC. Interleukin-10 in the vasculature: pathophysiological implications. *Curr Vasc Pharmacol.* 2022; 20: 230–243. doi: 10.2174/1570161120666211227143459.
4. dos Passos RR, Santos CV, Priviero F, Briones AM, Tostes RC, Clinton RW, et al. Immunomodulatory Activity of Cytokines in Hypertension: A Vascular Perspective. *Hypertension*; 2024; 81(7). Doi: 10.1161/HYPERTENSIONAHA.124.21712.
5. Haybar H, Bandar B, Torfi E, Mohebbi A, Saki N. Cytokines and their role in cardiovascular diseases, *Cytokine*, 2023; 169: 156261. <https://doi.org/10.1016/j.cyto.2023.156261>.
6. Hedayat M, Mahmoudi MJ, Taghvaei M, Nematipour E, Farhadi E, Esfahanian N, et al. Tumor Necrosis Factor-Alpha and Interleukin-6 Gene Polymorphisms in Iranian Patients with Ischemic Heart Failure. *Avicenna J Med Biotechnol.* 2018 Apr-Jun;10(2):105-109.
7. Li H, Chen C, Wang DW. Inflammatory Cytokines, Immune Cells, and Organ Interactions in Heart Failure. *Front Physiol.* 2021 Jul 1;12:695047. doi: 10.3389/fphys.2021.695047.
8. Loperena R, Beusecum JPV, Itani HA, Engel N, Laroumanie F, Xiao L, et al. Hypertension and increased endothelial mechanical stretch promote monocyte differentiation and activation: Roles of STAT3, interleukin 6 and hydrogen peroxide. *Cardiovasc. Res.* 2018;114:1547–1563. doi: 10.1093/cvr/cvy112
9. Schumacher SM, Naga Prasad SV. Tumor Necrosis Factor- α in Heart Failure: an Updated Review. *Curr Cardiol Rep.* 2018 Sep 26;20(11):117. doi: 10.1007/s11886-018-1067-7.
10. Silva LB, dos Santos Neto AP, Maia SMAS, dos Santos CG, Quidute IL, de Carvalho AAT, et al. The Role of TNF- α as a Proinflammatory Cytokine in Pathological Processes. *The Open Dentistry Journal.* 2019; 13: 332-338. Doi:10.2174/1874210601913010332.
11. Verma MK, Jaiswal A, Sharma P, Kumar P, Singh AN. Oxidative stress and biomarker of TNF-alpha, MDA and FRAP in hypertension. *J Med Life.* 2019;12:253–259. doi: 10.25122/jml-2019-0031.
12. Zhang H, Dhalla NS. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. *Int J Mol Sci.* 2024 Jan 16;25(2):1082. doi: 10.3390/ijms25021082.

Стаття надійшла 6.09.2024 р.