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Alteration of immune status during treatment with β-blockers in patients with essential hypertension

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Abstract

The balance of cytokines (IL-2, IL-10, IF-γ) in patients with essential hypertension before and after treatment with β-blockers was studied. 20 patients aged 45-65 years and diagnosed with essential hypertension (12 women, 8 men) were investigated. For the treatment of hypertension, patients received second-generation beta-selective β-blockers Egilok and Betalok Zok, and third-generation β-blocker Nebilet for one month. Patients performed their blood pressure measurements daily in the morning during I month. The content of interleukins (IL-2, IL-10, IF-γ) in the blood by the immune enzymatic ELISA method on a semi-automatic reader Stat Fax 3200 with RayBio, (USA) reagent was measured. The results of our studies show an increase in the level of CD4+ (IL-2) cytokines in the blood of the studied hypertensive patients, which coincides with the literature data on the important role of CD4+ pro-inflammatory cytokines in the pathogenesis of hypertension. After 1 month of treatment with β-blockers, the patient's arterial pressure and IL-2 level content in the blood decreased. These data indicate the important role of inflammation in the pathogenesis of hypertension and the anti-inflammatory effects of β-brokers, used in the treatment of hypertension.

KEY WORDS: essential hypertension; interleukins; β-blockers

Introduction

Epidemiological and experimental studies revealed a relationship between biochemical markers of systemic inflammation and diseases of the cardiovascular system, such as atherosclerosis, heart failure, and hypertensive disease [1]. The relationship between the regulatory systems of arterial hypertension, such as the renin-angiotensin system, the sympathetic nervous system, and proinflammatory cytokines, has been determined. As is known, pro-inflammatory cytokines affect vascular function, cause structural and functional changes in endothelial cells, regulate the release of vasoactive factors by the endothelium (endothelin, nitric oxide, NOS-mRNA [2] and in this way participate in blood pressure regulation.

Stimulation of sympathetic neurons innervating secondary lymphoid organs suppresses inflammation in various chronic diseases by regulating cytokine secretion [2]. This mechanism is quite important and has been used in the treatment of various chronic inflammatory diseases. Neuro-immune mechanisms involve adrenergic receptors, including β-adrenoreceptors, which are expressed on various (innate and adaptive) immune cells. In order to control ″inflammation″, the neuro-signaling system through β-adrenoreceptors limits the release of inflammatory cytokines by macrophages and dendritic cells, as well as the activated T cells.

We studied the balance of cytokines (IL-2, IL-10, IF-γ) in patients with essential hypertension before and after treatment with beta-blockers.

Materials and Methods

20 patients aged 45-65 years and diagnosed with essential hypertension (12 women, 8 men) were studied.

Inclusion criteria for hypertensive patients – elevated blood pressure (with a sitting position ≥140/90±10 mm Hg) during 3 consecutive measurements over 4 weeks.

Exclusion criteria from the study were polycystic ovary syndrome, ovariectomy, hormone therapy, excessive alcohol consumption (more than 20 g per day), taking estrogen replacement drugs, glucocorticoids, aspirin, calcium channel blockers, diabetes mellitus, and kidney diseases.

For the treatment of hypertension, patients received second-generation be-

ta-selective β-blockers Egilok and Betalok Zok, and third-generation β-blocker Nebilet for one month.

Patients performed their blood pressure measurements daily in the morning; Initial (before treatment) and final (after treatment) blood pressure values were analyzed.

We collected blood from patients before treatment and 1 month after treatment. Collected blood samples were stored at – 80°C and just before analysis thawed at 4°C in a refrigerator. We measured the content of interleukins (IL-2, IL-10, IF-γ) in the blood by the immune enzymatic ELISA method on a semi-automatic reader Stat Fax 3200 with RayBio, (USA) reagent.

Statistical Analysis

Statistical analysis was performed using the ″Statistical Package for Social Sciences (SPSS) for Windows (SPSS version 11.0)″. Results were expressed as means ± SD. A confidence limit of 0.05 ($P<0.05$) was selected for statistical confidence.

Results

Fig. 1. shows the blood pressure values of the studied patients with essential hypertension before and after treatment with β-blockers. As can be seen from diagram 1, blood pressure indicators of the studied patients tend to decrease after treatment with β-blockers.

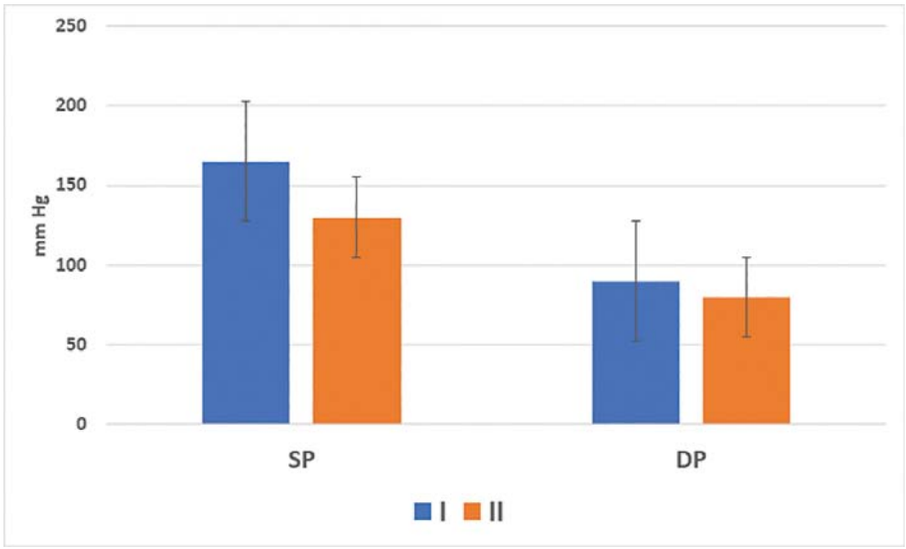

Fig. 1. *Blood pressure indicators of studied patients before and after treatment with β-blockers. (Series 1 – hypertensive patients before treatment; Series 2 – hypertensive patients after treatment).*

Fig. 2. shows the magnitude of the deviation from the maximum value of the normal content of cytokines (IF-γ, IL-2, IL-10) (optimal index – IF-γ – 0-5pg/ml; IL-2 – 0-10pg/ml; IL – 10 – 0-31pg/ml) in the blood of the studied patients before and after treatment with β-blockers.

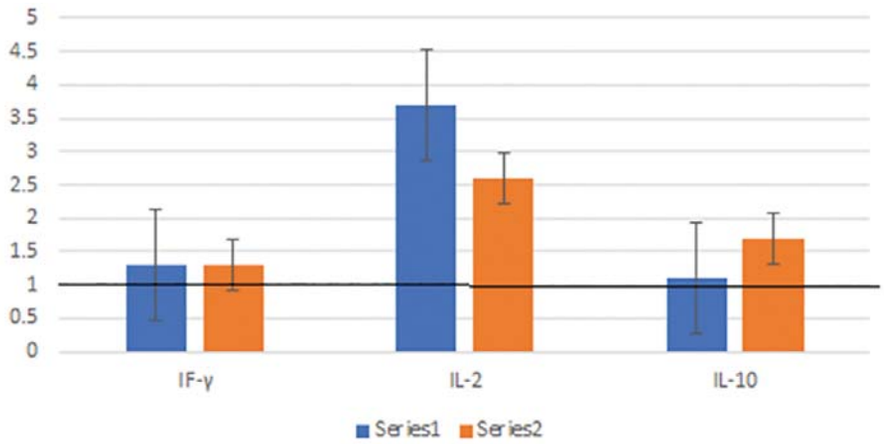

Fig. 2. *The magnitude of the deviation from the maximum value of the normal content of cytokines (IF-γ, IL-2, IL-10) (optimal index – IF-γ – 0-5pg/ml; IL-2 – 0-10pg/ml; IL – 10 – 0-31pg/ml) in the blood of the studied patients before and after treatment with β-blockers. (Series 1 – hypertensive patients before treatment; Series 2 – hypertensive patients after treatment). – optimal index of the cytokines.*

As can be seen from the figure, in the blood of the hypertensive patients studied by us before the treatment the levels of IF-γ and IL-10 did not importantly vary from the optimal levels, while IL-2 was 3-4 times higher than the optimal level. After 1 month of

treatment of hypertensive patients with β-blockers, the content of F-γ and IL-10 in the blood almost did not change compared to the initial values, while the content of IL-10 statistically significantly decreased by 30% compared to the initial values.

Discussion

As is known, inflammation is a key component in the pathophysiology of hypertension, it determines not only hypertension development and/or progression but also leads to end-organ damage [3,4]. Metabolic/chemical, mechanical (wall stretch), or infectious endothelial aggressions trigger complex immune reactions, leading to a pro-inflammatory state [5]. There are data that patients with essential hypertension have an altered profile of pro – and anti-inflammatory cytokines [6].

In studies dedicated establishment of the role of subtypes of T cells in hypertension and the mechanisms by which they contribute to this disease, was shown that mice lacking CD8+T cells were protected from hypertension, whereas mice lacking CD4+T cells or MHC class II were not [7]. An interesting study by Youn et al. [8] compared circulating T cell phenotypes in newly diagnosed hypertensive patients to age – and sex-matched controls and found that the number of circulating pro-inflammatory CD8+T cells is increased in humans with hypertension. These cells produce increased amounts of IFN-γ, TNF-α, and the cytotoxic molecules granzyme B and perforin compared with CD8+T cells from normal subjects. There is also evidence that CD4+T cells are activated in hypertension and likely play an important role.

The regulation of the functional activity of lymphocytes, the protective and damaging effect of T cell antibodies in the immune system, is based on the interaction of immune cells with mediators of the nervous and endocrine systems. Several autoregulatory mechanisms have been developed that ensure the maintenance of homeostasis of these systems and regulation of the immune response in various diseases [9,10]. These regulatory mechanisms include the modulation of the cellular membrane-surface receptors, in particular, β-adrenergic receptors. Early data of radioligand binding analysis confirmed the expression of the β-adrenergic receptor on both the human and the murine T cell populations, of which the β2 adrenergic receptor subtype is predominant; scarce evidence supports the expression of a high-affinity β1 adrenergic receptor on T cells [11,12]. It was shown that β-adrenergic blockers can alter the mitogenic response of lymphocytes [13,14], increase their proliferation and differentiation rate, and therefore change the distribution of lymphocyte subclasses [15].

The results of our studies show an increase in the level of CD4+ (IL-2) cytokines in the blood of the studied hypertensive patients, which coincides with the literature data on the important role of CD4+ pro-inflammatory cytokines in the pathogenesis of hypertension [6,7]. Possibly, it is related to the regulatory effect of IL-2 associated with the synthesis and secretion of other cytokines (IL-4, IL-6, IFN-γ, CSFs, TNF-α) [16]. After 1 month of treatment with β-blockers, the patient's arterial pressure and IL-2 level content in the blood decreased. These data indicate the important role of inflammation in the pathogenesis of hypertension and the anti-inflammatory effects of β-blokers, used in the treatment of hypertension.

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