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Dynamics of parameters of proinflammatory activation in patients with hypertension under influence of candesartan therapy

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Key words: *Hypertension, Proinflammatory Activation, C-Reactive Protein, Soluble Form Of Intercellular Adhesion Molecule-1, Tumor Necrosis Factor-alfa, Candesartan.*

Aim. Proinflammatory activation is one of the possible pathogenetic mechanisms of formation and progression of hypertension. 107 patients with essential hypertension (EH) II stage was included into the study of the pro-inflammatory activation.

Methods and results. Levels of C-reactive protein (CP), α-tumor necrosis factor (α-TNF) and soluble form of intercellular adhesion molecule-1 (sICAM-1) in the serum were studied by ELISA before and after 12 weeks of treatment with candesartan. 31 healthy subjects were included in the control group. It is found that C-reactive protein in 5,18 times ($p<0,05$), α-tumor necrosis factor on the 39,04% ($p<0,05$) and sICAM-1 to 41, 87% ($p<0,05$) higher in hypertensive patients with stage II than those of the control group. Significant reductions of CRP in the blood serum by 70,33%, α-TNF – by 19,94% and sICAM-1 in serum by 18,46% compared to baseline ($p<0,05$) were found under the influence of candesartan therapy.

Conclusion. These data indicate the presence of activation of proinflammatory processes in hypertensive patients with significant progression according to the degree of blood pressure and additional anti-inflammatory properties of candesartan.

Динаміка параметрів прозапальної активації у хворих на гіпертонічну хворобу під впливом терапії кандесартаном

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Прозапальна активація є одним із можливих патогенетичних механізмів становлення і прогресування артеріальної гіпертензії. З метою дослідження прозапальної активації у 107 хворих на гіпертонічну хворобу II стадії імуноферментним методом вивчили рівень С-реактивного протеїну, α-фактора некрозу пухлини та розчинної форми міжклітинної молекули адгезії-1 у сироватці крові до і після 12 тижнів терапії кандесартаном. Виявили, що у хворих на гіпертонічну хворобу II стадії рівень С-реактивного протеїну в 5,18 раза ($p<0,05$), α-фактору некрозу пухлини на 39,04% ($p<0,05$) та розчинної форми міжклітинної молекули адгезії-1 на 41,87% ($p<0,05$) вище у порівнянні з особами групи контролю. Після терапії кандесартаном виявили достовірне зменшення вмісту С-реактивного протеїну в сироватці крові на 70,33%, α-фактора некрозу пухлини – на 19,94%, розчинної форми міжклітинної молекули адгезії-1 у сироватці крові на 18,46% у порівнянні з вихідними показниками ($p<0,05$). Результати свідчать про активацію прозапальних процесів у хворих на гіпертонічну хворобу із суттєвим прогресуванням відповідно до зростання рівня артеріального тиску, а також про додаткові протизапальні властивості кандесартану.

Ключові слова: *гіпертонічна хвороба, прозапальна активація, С-реактивний протеїн, розчинна форма міжклітинної молекули адгезії-1, α-фактор некрозу пухлини, кандесартан.*

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Динамика параметров провоспалительной активации у больных гипертонической болезнью под влиянием терапии кандесартаном

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Провоспалительная активация – один из возможных патогенетических механизмов становления и прогрессирования артериальной гипертензии. С целью исследования провоспалительной активации у 107 больных гипертонической болезнью II стадии иммуноферментным методом изучен уровень С-реактивного протеина, α-фактора некроза опухоли и растворимой формы межклеточной молекулы адгезии-1 в сыворотке крови до и после 12 недель терапии кандесартаном. Установлено, что у больных гипертонической болезнью II стадии уровень С-реактивного протеина в 5,18 раза ($p<0,05$), α-фактора некроза опухоли на 39,04% ($p<0,05$) и растворимой формы межклеточной молекулы адгезии-1 на 41,87% ($p<0,05$) выше по сравнению с лицами группы контроля. После терапии кандесартаном отмечено достоверное уменьшение содержания С-реактивного протеина в сыворотке крови на 70,33%, α-фактора некроза опухоли – на 19,94%, растворимой формы межклеточной молекулы адгезии-1 в сыворотке крови на 18,46% по сравнению с исходными показателями ($p<0,05$). Результаты свидетельствуют об активации провоспалительных процессов у больных гипертнонической болезнью с существенным прогрессированием по мере роста степени артериального давления, а также о дополнительных противовоспалительных свойствах кандесартана.

Ключевые слова: *гипертоническая болезнь, провоспалительная активация, С-реактивный протеин, растворимая форма межклеточной молекулы адгезии-1, α-фактор некроза опухоли, кандесартан.*

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Arterial hypertension (AH) takes one of the leading places in the structure of cardiac pathology. It is complex medical and social problem because of its prevalence, early development of complications. Pathogenetic mechanisms of hypertension are characterized by heterogeneity. Recent studies suggest possible role of proinflammatory activation in the development of this disease [2,4,15]. First of all, it caused by biomechanical stress due to increased blood pressure, as the experimental and clinical studies have shown. This way is one of the incentives to increased production of CRP and pro-inflammatory cytokines, including α-TNF [11]. On the other hand, today's medical science has enough data about the ability of

inflammatory markers to modulate the structure and function of cardiovascular system through a number of mechanisms [8–10]. Many studies have shown that increased activity of plasma CRP, TNF-α promotes hypertrophy, fibrosis, apoptosis, and as a result – the occurrence of cardiac dysfunction [13], whereas sICAM-1 is one of the most informative laboratory markers of endothelial dysfunction [12]. In recent years large number of messages about the regression of pro-inflammatory activation in patients with essential hypertension (EH) that leads to a significant reduction of risk of cardiovascular events and to the more favorable course of the disease appeared in medical literature [6]. Unfortunately, many studies do not assess the effectiveness of different groups of antihypertensive drugs on the impact of chronic inflammation and endothelial dysfunction [5,16].

The aim of this study was to determine the main features of pro-inflammatory activation in patients with hypertension and to investigate the effect of therapy with angiotensin II receptor antagonist candesartan on the studied processes.

Objects and methods

The study included 107 patients with stage II essential hypertension without clinically significant comorbidity. 66 women and 41 men, aged 31 to 75 years were recruited into this study (mean age 54,3±0,98 years). The diagnosis of essential hypertension was established according to the recommendations of the Ukrainian Society of Cardiology (2012) [17].

The inclusion criteria in the study were: diagnosed arterial hypertension stage II, age of participants from 18 to 75 years and informed consent of patient for participation in the study.

The exclusion criteria were the following: symptomatic arterial hypertension; presence of any form of coronary heart disease; chronic heart failure III-IV functional class (NYHA); clinically significant arrhythmias and conduction disturbances; chronic renal failure; diabetes; chronic inflammatory diseases; systemic connective tissue disease; other somatic pathology, that is accompanied by changes in the studied parameters and can thus affect findings.

Depending on the degree of hypertension patients in the observation group were divided into 3 groups: the 1st included 55 patients with mild hypertension, 2nd – 42 patients with moderate hypertension, 3rd – 10 patients with severe hypertension. All patients with AH were prescribed angiotensin II receptor antagonist candesartan in a daily dose of 8–16 mg. 12-week treatment period was completed by 105 patients.

Control group consisted of 31 almost healthy persons. This group was comparable to the observation group by sex and age. Each patient gave voluntary written informed consent for the participation in the study.

Study of the C-reactive protein, α-tumor necrosis factor and sICAM-1 levels in serum was performed by ELISA OD «Digiscan Microplate Reader». Level of CRP was measured with kit «Microwell ELISA» produced by «Diagnostic Automation, Inc.» according to the applied instructions. Serum level of α-tumor necrosis factor was measured with kit «Human TNFα ELISA» produced by «Diaclone» (France) according to the applied instructions. Level of sICAM-1 was measured with kit «sICAM-1 ELISA KIT» produced by «Diaclone» (France) according to applied to the kit instructions. Studied values were given like sample mean ± standard error of the sample mean. A probability difference of quantitative data was established by checking the «null» hypothesis using the P criterion. Student's t-test was used to estimate the probability of difference in case of parameter's paired changes. Criterion Mann-Whitney was used to verify the statistical significance of differences in case of deviation from the Gaussian distribution. All statistical procedures were performed in software packages «STATISTICA® 6.0 for Windows» (StatSoft Inc.) and «Microsoft® Excel 2007» (Microsoft®).

Results and discussion

The main features of the parameters characterizing the pro-inflammatory activation in patients with essential hypertension with different degrees of AH severity and in patients of the control group are presented in *table 1*.

Generally, significant increase in serum level of C-reactive protein in 5,18 times ($p<0,05$) and increased level of α-tumor necrosis factor up to 39,04% ($p<0,05$) was observed in patients with EH in compare with those in the control group. It is worth noting also that significant increase of the level of s-ICAM-1 in serum in patients with EH was seen compared to subjects up to almost 41,87% ($p<0,05$).

By studying the activation parameters of immune-inflammatory processes in patients with EH depending on the degree of hypertension was found that with increasing the degree of hypertension was observed a progressive increasing of serum levels of CRP and TNF-α. Dynamics of changes in these parameters was quite distinct. Thus, in patients with 2 degree hypertension C-reactive protein and α-TNF levels were in 2.24 times ($p<0,05$) and at 21,14% ($p<0,05$) higher compared to the patients with mild hypertension. Subjects with severe hypertension were characterized by serum CRP and TNF-α levels respectively 24,19% ($p<0,05$) and 15,14% ($p<0,05$) higher than patients with 2 degree AH. The most significant differences were found between the studied parameters in patients with 1st and 3rd degrees of AH – 2,78 times ($p<0,05$) for CRP level and 39,48% ($p<0,05$) for α-tumor necrosis factor (*table 1*).

Table 1

Performance of immune-inflammatory activation in hypertensive patients with different degrees of hypertension

Indicator	Patients with EH				Control group (n=31)
	1st degree AH (n=55)	2nd degree AH (n=42)	3rd degree AH (n=10)	Generally in group (n=107)	
CRP, mg/l	1,79±0,12	4,01±0,39*#	4,98±0,77*#§	3,63±0,35*	0,70±0,16
TNFα, pg/ml	129,37±3,61*	156,72±6,29*#	180,44±16,8*#§	150,05±5,90*	107,92±2,41
s-ICAM-1, pg/ml	800,90±16,26*	875,77±19,53*#	946,26±29,94*#§	838,06±13,63*	590,72±41,21

NB: * – $p<0,05$ compared to the control group; # – $p<0,05$ compared to the patients with 1st degree hypertension; § – $p<0,05$ compared to the patients with 2nd degree hypertension.

Table 2

Dynamics of the immune-inflammatory activation in hypertensive patients with different degrees of hypertension after 12 weeks of the candesartan treatment

Indicator	Before treatment			After 12 weeks of treatment		
	1st degree AH (n=22)	2nd degree AH (n=9)	3rd degree AH (n=2)	1st degree AH (n=22)	2nd degree AH (n=9)	3rd degree AH (n=2)
CRP, mg/l	1,83±0,14	3,85±0,41	4,78±0,34	0,96±0,14*	1,22±0,23*	3,15±0,20*
TNFα, pg/ml	136,8±4,55	154,5±5,45	184,2±12,8	109,9±2,73*	113,7±5,16*	151,6±13,3*
s-ICAM-1, pg/ml	786,4±16,0	881,9±27,3	952,6±33,4	693,8±7,55*	693,7±9,14*	747,3±11,3*

NB: * – p<0,05 compared to those before treatment.

Severity of hypertension increase was characterized by increase of the concentration of the intercellular adhesion molecule-1 soluble form. Thus, in patients with 1st degree hypertension s-ICAM-1 serum level was higher at 35,58% (p<0,05), in patients with moderate hypertension – at 48,25% (p<0,05) and in patients with 3rd degree hypertension - at 60,19% (p<0,05) compared to healthy subjects. Reliable differences were reported between subgroups of patients with EH with different degrees of hypertension. Particularly, level of s-ICAM-1 was significantly higher in patients with EH with 3rd degree hypertension compared to the patients with 2nd degree hypertension up to 8,05% (p<0,05), and to the patients with mild hypertension – to 18,15% (p<0,05).

As the Figure 1 shows, there was a significant reduction of serum CRP at 70,33% compared to the baseline values through 12 weeks of candesartan therapy. Level of TNF-α under the influence of 12-week candesartan therapy was significantly decreased at 19,94% compared to the original data. The positive effect of antihypertensive treatment with angiotensin II receptor antagonist candesartan therapy that is characterized by decreased levels of CRP and α-TNF in serum in the end of the 12-week treatment demonstrates significant decrease in immune-inflammatory activity in patients with EH.

After 12 weeks of candesartan therapy there was observed the significant reduction of sICAM-1 in serum at 18,46% compared to the baseline values. Reduced activity of sICAM-1 in serum at the end of 12 weeks of candesartan treatment reflects a significant decrease in production of proinflammatory markers of endothelial dysfunction. At the same time, it should be noted that, despite the significant reduction in the above parameters, the complete normalization parameters of immune-inflammatory activation was not observed, that, however, may be caused by insufficient duration of observation (*fig. 1*).

Dynamics of inflammatory activation indicators under the influence of candesartan treatment in hypertensive patients with different degrees of hypertension is presented in *table 2*. All patients had significant positive changes in serum levels of C-reactive protein, TNF-α and sICAM-1 on the background of ongoing drug therapy.

Thus, in patients with 1 degree hypertension CRP levels after 12 weeks of therapy was significantly decreased at 47,54% (p<0,05), α-TNF – at 19,66% (p<0,05), a soluble form of intercellular adhesion molecule-1 – at 11,78% (p<0,05) respectively. In patients with moderate hypertension above

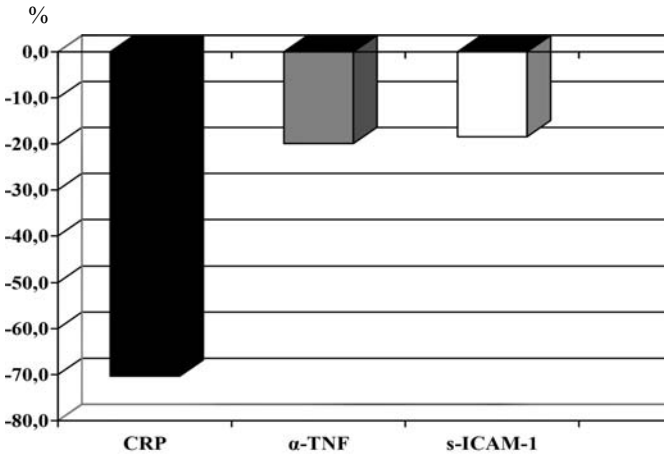

Fig. 1. Dynamics of decreasing the level of proinflammatory activation after 12 weeks of candesartan treatment.

parameters was significantly decreased at 68,31% (p<0,05), 26,41% (p<0,05) and 21,34% respectively. Similar changes were observed in patients with 3rd degree hypertension – the level of CRP in serum under the influence of candesartan therapy was significantly decreased at 34,10% (p<0,05), α-tumor necrosis factor level was decreased at 17,70% (p<0,05) and the level of s-ICAM-1 in serum was decreased at 21,55% (p<0,05).

Thus, the data indicate that use of angiotensin II receptor antagonist candesartan allows avert violations of immune-inflammatory activation observed in patients with essential hypertension.

Conclusions

1. In patients with hypertension stage II was observed the activation of inflammatory processes, and as the result are the increasing of serum level of C-reactive protein (5,2 times), α-tumor necrosis factor (at 39,04%) and soluble form intercellular adhesion molecule-1 (to 41,87%) compared to the control group.

2. The proinflammatory activation in patients progresses significantly by decreasing blood pressure.

3. Candesartan has additional anti-inflammatory properties. This is confirmed by significantly reduction in levels of C-reactive protein (at 70,33%), α-tumor necrosis factor (at 19,94%) and the soluble form of intercellular adhesion molecule-1 (at 18,46%) in serum after 12 weeks of treatment.

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