Effects of antihypertensive treatment on systemic inflammation, oxidative stress and proinflammatory cytokine levels

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Abstract

Hypertension in its origin is a heterogeneous and multisystemic disease. Evaluation of oxidative stress activity based on the level of 8-iso-PGF2α, proinflammatory activity based on tumour necrosis factor-α, its type I soluble receptor, and C-reactive protein levels is relevant for further understanding of pathogenesis of hypertension and improvement of the early diagnostics of heart failure. 186 hypertensive patients were observed during a 2-months course of treatment, aged 30 to 65 years. Serum levels of 8-iso-PGF2α (n = 34), tumour necrosis factor-α and its type I soluble receptor were determined by ELISA before and after course of treatment. C-reactive protein level was determined by biochemical method. The control group included 16 clinically healthy individuals, aged 27 to 55 years. Hypertensive patients enrolled into the study were randomized into three groups that received different protocols of combined anti-hypertensive therapy: I clinical group – a combination of bisoprolol and indapamide, II – a combination of lacidipine and candesartan, III – a combination of fosinopril sodium and hydrochlorothiazide. On the background of combined antihypertensive therapy, we observed favourable dynamics of 8-iso-PGF2α, tumour necrosis factor-α and its type I soluble receptor, and C-reactive protein levels. Taking into account the significance of the correlations revealed, a one-factor dispersion analysis was applied which allowed us to determine the influence of the grade and duration of hypertension on the dynamics of the studied parameters. It has been found that the grade of hypertension is related to an increase in TNF-α and 8-iso-PGF2α serum levels, but not in TNF-α type I soluble receptor, and the duration of hypertension is related to an increase in C-reactive protein, TNF-α and its type I soluble receptor levels, with no relation to the level of 8-iso-PGF2α. Thus, oxidative stress possibly promotes the activation of potentially damaging immune mechanisms mediated by proinflammatory cytokines, nonspecific inflammation and drives the further progression of lesions in the target organs.

Keywords: 8-iso-PGF2α; tumour necrosis factor-α; type I soluble receptor; C-reactive protein; blood pressure.

Introduction

Hypertension occupies one of the leading places in the structure of cardiac pathology and presents a complex medical and social problem considering its high prevalence and the early development of complications. Hypertension in its origin is a heterogeneous and multisystemic disease. In the last decade, the role of immune-inflammatory activation mediated by proinflammatory cytokines, systemic inflammation and oxidative stress (OS) in the pathogenesis of cardiovascular diseases, including hypertension, has been actively studied (Bautista et al., 2005; Mahmud & Feed, 2005). The term “oxidative stress” (OS) is understood as a condition in which the amount of free radicals formed in the body is significantly higher than the activity of endogenous antioxidant systems that ensure their elimination (Kovalyova et al., 2005; Allison, 2016). It has been suggested that OS and immune-inflammatory changes participate in the pathogenesis of cardiovascular dysfunction, are interrelated and can induce each other, forming a vicious circle (Kovalyova et al., 2015).

Among the proinflammatory cytokines, tumour necrosis factor-α (TNF-α) deserves special attention in the context of hypertension. Firstly, this is due to the fact that, as shown by experiments and an insignificant number of clinical studies, hemodynamic stress caused by increased blood pressure (BP) is one of the stimuli to increase production and release of pro-inflammatory cytokines, including TNF-α, into the bloodstream (Goldhaber et al., 1996; Grainger, 2007). Secondly, it is due to existing data on the ability of this cytokine to modulate the structure and function of the cardiovascular system through a number of mechanisms. As an example, TNF-α is able to suppress myocardial contractility. This may be due to blocking of β-adrenergic signals, reduction of the content of nitric oxide in the heart, or changes in intracellular calcium homeostasis (Goldhaber et al., 1996). TNF-α can also induce structural changes in the myocardium of patients with hypertension and chronic heart failure, such as cardiomyocyte hypertrophy and interstitial fibrosis (Kovalyova & Ashcheulova, 2003). In addition, TNF-α promotes apoptosis of cardiomyocytes, and also activates metalloproteinases and depresses the expression of their inhibitors, thus promoting cardiac remodeling (Li et al., 2000; Haider et al., 2002) and eventually leading to cardiac dysfunction.

In healthy people, TNF-α is barely detectable in serum. Its level increases in infections under the influence of bacterial endotoxins (Vasan, 2006). There are two types of active receptors for TNF-α on the surface of almost all nuclear cell types that can virtually be cytokine targets. Soluble forms of receptors, which are considered endogenous inhibitors of TNF-α, are formed by separating the extracellular fragments of active receptors (Simbirtsev, 2013). TNF-α type I receptor (sTNF-α RI) is the main mediator of cytokines’ biological activity.

C-reactive protein (CRP) is a recognized marker of the acute phase of inflammation. With the advent of new highly sensitive techniques for its quantitative determination, it attracts increasing attention of cardiologists. This is due to the data on elevated CRP levels having a possible predictive role for the development of the set of cardio- and cerebrovascular complications such as congestive heart failure, myocardial infarction, stroke, sudden cardiac death and peripheral vascular disease (Sproston & Ashworth, 2018). The prognostic value of a high CRP level in patients with stable
angina pectoris, acute coronary syndrome and myocardial infarction has been shown (Melnikov et al., 2019; Melnikov et al., 2020). However, it should be noted that there were fewer reports on the diagnostic value of this systemic inflammation marker in essential hypertension, and there is insufficient evidence of the relationship between CRP, TNF-α and 8-isoprostane (8-isoprostane) as the main OS marker in patients with hypertension from the clinical studies.

According to current data, detection of 8-isoprostane in blood or urine is a sensitive method for evaluating the intensity of OS. 8-isoprostane is one of the most reliable and specific markers that allows us to assess the level of free radical production in the human organism in a wide spectrum of different diseases. 8-isoprostane is a product of metabolism in reactions of arachidonic acid peroxidation that is isomeric to prostaglandin F2α. Its level is proportional to the amount of free radicals formed. This substance belongs to the family of eicosanoids that are a product of the non-enzymatic (free radical) oxidation of phospholipids of cellular bioremembranes (Lawson et al., 1999; Cracowski et al., 2000). There is evidence (Greco et al., 2000; Czereska et al., 2016) of an increase in the level of 8-isoprostane in neurodegenerative diseases, coronary heart disease and hypertension. A significant increase in the level of 8-isoprostane has been observed in a number of conditions characterized by increased oxidative activity, particularly in tobacco smoking (Morrow et al., 1995), diabetes mellitus (Davi et al., 1999), hypercholesterolemia (Davi et al., 1997).

Evaluation of OS activity based on the levels of 8-isoprostane, TNF-α and its soluble type I receptor, and C-reactive protein levels might allow us to reveal the correlations between the level of OS, immune activation and nonspecific inflammation in the human organism, which is relevant for further understanding of pathogenesis of hypertension and improvement of the early diagnostics of heart failure.

The purpose of this research was to assess the activity of proinflammatory cytokines and C-reactive protein serum levels (as independent markers of systemic inflammation) in the context of oxidative stress development, depending on the severity and duration of hypertension, and their changes under the influence of combined antihypertensive therapy.

Materials and methods

The study was conducted in accordance with the current ethical requirements. The protocol of the study was approved by the Committee of Bioethics of Kharkiv National Medical University, Department of Propedeutics of Internal Medicine No. 2 and Nursing Care. Informed consent was obtained from all participants of the study. 202 subjects were examined in the in-hospital setting, including 186 patients with essential hypertension of the European Society of Cardiology (ESC) / European Society of Hypertension (ESH) (2018) were used for verification of the diagnosis.

A clinical examination was performed using one-way analysis of variance (ANOVA) with the calculation of Fisher test (F), Wilcoxon T-test was used for paired intragroup analysis, with differences considered significant at P < 0.05.

Results

The study included a total of 202 patients, of whom 50% (n = 102) were men and 50% (n = 100) were women. The mean age of the patients was 54.7 ± 5.8 years. The majority of patients (76%) were diagnosed grade 1 hypertension, 8% – of grade 2, and 16% – of grade 3. The level of 8-isoprostane as a main marker of OS was assessed in 10, 14, and 10 patients of the three clinical groups, respectively. The aforementioned parameters were reassessed after two months of treatment. I clinical group (n = 102) received a combination of a β-adrenoblocker (BAB) and diuretic (D) (bisoprolol 2.5–10.0 mg/day, and indapamide 1.25–2.5 mg/day). The daily dose of bisoprolol was administered by continuous slow titration, starting with low doses of 1.25 mg/day. Gradually the dose was increased to the maximum tolerated or target dose under the control of clinical parameters, especially blood pressure and heart rate (HR). II clinical group (n = 30) received a combination of a calcium channel blocker (CCB) and angiotensin receptor blocker (ARB) (lacidipine 2, 4 mg and candesartan 4, 8 and 16 mg). III clinical group (n = 54) received a combination of an angiotensin-converting enzyme inhibitor (ACEI) and diuretic (D) (fosinopril sodium 20 mg/day and hydrochlorothiazide 12.5 mg/day). The levels of 8-isoprostane were assessed in 10, 14, and 10 patients of the three clinical groups, respectively. The dose of medications was individually up-titrated in cases of need during the course of treatment. As one can see (Table 1) the different clinical groups were comparable in terms of age, gender structure and clinical course of hypertension.

Table 1

Comparative characteristic of clinical groups of patients with hypertension

<table>
<thead>
<tr>
<th>Parameters</th>
<th>I clinical group (n = 102)</th>
<th>II clinical group (n = 30)</th>
<th>III clinical group (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male, n 20</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Female, n 82</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>Age, years</td>
<td>54.5 ± 5.4</td>
<td>54.7 ± 5.8</td>
<td>54.5 ± 5.4</td>
</tr>
<tr>
<td>Hypertension, years</td>
<td>9.6 ± 0.7</td>
<td>10.7 ± 1.4</td>
<td>9.7 ± 1.4</td>
</tr>
<tr>
<td>Hypertension grade, %</td>
<td>1</td>
<td>17.6</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28.4</td>
<td>26.7</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>54.0</td>
<td>50.0</td>
</tr>
<tr>
<td>New York Heart Association class, %</td>
<td>0</td>
<td>11.9</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>19.6</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>65.6</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>2.9</td>
<td>3.3</td>
</tr>
</tbody>
</table>

The results were statistically processed using Statistica 7.0 software packages (StatSoft Inc., USA). Mean values and their standard deviation (± SD) are presented in the text and tables. The intergroup analysis was performed using one-way analysis of variance (ANOVA) with the calculation of Fisher test (F). Wilcoxon T-test was used for paired intragroup analysis, with differences considered significant at P < 0.05.

Analysis of the activity of proinflammatory cytokines showed a significant increase in the levels of TNF-α in patients with hypertension compared to control: 187 ± 18.1 vs 132 ± 3.4 pg/mL, respectively (P < 0.001). A similar tendency was observed with respect to soluble fraction of TNF-α receptor. The value of sTNF-αRI in hypertension also exceeded that in the control group: 2.14 ± 0.28 vs 1.20 ± 0.60 pg/mL, respectively (P < 0.001). An increase in the serum 8-isoprostane was also found in patients with hypertension compared to healthy controls: 17.2 ± 3.1 vs 14.1 ± 0.25 pg/mL, respectively (P < 0.05). The level of 8-isoprostane in hypertensive patients was 12.2 times higher compared to the control group. Considering the available data on the importance of CRP as a marker of systemic inflammation in cardiovascular pathology and as a predictor of development of heart failure (HF) and hypertension, we assessed the levels of serum CRP in patients with hypertension and revealed values exceeding the control group (6.23 ± 0.33 mg/L). In order to elucidate the influence of not only the presence, but also the grade of increase in blood
pressure on the expression of TNF-α, sTNF-αRI, CRP, and also to evaluate the presence and level of oxidative stress, all patients were divided into groups depending on the grade of hypertension (Table 2).

Unlike TNF-α and 8-isoprostane, CRP levels did not significantly differ between groups. As one can see from Table 2, in patients with hypertension, a 3.2-fold, 7.1-fold and 18.4-fold increase (grades 1, 2, and 3, respectively) in the 8-isoprostane serum levels was observed compared to the control group. When comparing the levels of 8-iso-PG2α in patients with different grades of hypertension, it was revealed that serum 8-isoprostane increased as the disease progressed: in patients with grade 3 hypertension, it exceeded by 5.8 times the value in patients with grade 1 and 2.6 times – in those with grade 2.

The levels of TNF-α, sTNF-αRI, 8-isoprostane, and CRP in the examined patients depended not only on the grade, but also on the duration of hypertension (Table 3).

Rank correlation analysis was performed to determine the relationship between blood pressure and levels of TNF-α, CRP and 8-isoprostane. The correlation coefficient (r) between the grade of hypertension and serum TNF-α levels was 0.204 (P = 0.125), for sTNF-αRI – r = –0.01 (P = 0.97), for 8-isoprostane – r = 0.11 (P = 0.94), for CRP – r = 0.02 (P = 0.44). Correlation coefficients with the duration of hypertension were: for TNF-α – r = –0.24 (P = 0.17), for sTNF-αRI – r = 0.17 (P = 0.53), for 8-isoprostane – r = 0.01 (P = 0.95), for CRP – r = 0.32 (P = 0.74). Taking into account the insignificance of the correlations revealed, a one-factor dispersion analysis was applied to determine the influence of the grade and duration of hypertension on the dynamics of the studied parameters.

It was found that the grade of hypertension was related to the serum levels of TNF-α and 8-isoprostane (P = 0.02, P = 0.004, respectively), but not sTNF-αRI and CRP, and the duration of hypertension was related to the levels of TNF-α, sTNF-αRI and CRP (F = 6.72, P = 0.003; F = 2.34, P = 0.006; F = 9.96, P = 0.002, respectively), with no relation to the level of 8-isoprostane. Analysis of the relationships between the levels of 8-isoprostane, TNF-α and sTNF-αRI has shown no significant correlations.

In the first group of patients on the background of treatment with bisoprolol and indapamide, the mean levels of TNF-α significantly decreased to 70.2 pg/mL compared to baseline before treatment, showing a 61.0% reduction (Table 4). The mean levels of soluble sTNF-αRI, which is a natural inhibitor of TNF-α, increased to 0.24 ng/mL (11.1%) after treatment. A significant decrease in the TNF-α/sTNF-αRI ratio by 34.4 (64.9%) indicated a predominant increase in the level of sTNF-αRI along with decrease in TNF-α. Since soluble forms of receptors act as natural antagonists of TNF-α, a decrease in this ratio reflects suppression of autoimmune and apoptotic activity in patients after treatment.

### Table 2

Levels of TNF-α, sTNF-αRI, CRP, and 8-isoprostane depending on the grade of hypertension (x ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>1 grade</th>
<th>2 grade</th>
<th>3 grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α, pg/mL</td>
<td>13.2 ± 3.4</td>
<td>1120 ± 26.1</td>
<td>1420 ± 27.2***</td>
<td>1170 ± 18.9*</td>
</tr>
<tr>
<td>sTNF-αRI, ng/mL</td>
<td>1.20 ± 0.60</td>
<td>2.02 ± 0.22***</td>
<td>2.13 ± 0.16</td>
<td>2.19 ± 0.08*</td>
</tr>
<tr>
<td>8-isoprostane, ng/mL</td>
<td>1.41 ± 0.25</td>
<td>4.48 ± 0.55**</td>
<td>10.00 ± 0.99***</td>
<td>25.90 ± 2.87*****</td>
</tr>
<tr>
<td>CRP mg/L</td>
<td>6.25 ± 0.33</td>
<td>6.25 ± 0.57</td>
<td>6.01 ± 0.77</td>
<td>6.36 ± 0.45</td>
</tr>
</tbody>
</table>

Note: * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs control group; * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs patients with grade 1 hypertension; * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs patients with grade 2 hypertension.

### Table 3

Levels of TNF-α, sTNF-αRI, CRP, and 8-isoprostane in patients with different duration of hypertension, yrs (x ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>≤ 5</th>
<th>5-10</th>
<th>&gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α, pg/mL</td>
<td>13.2 ± 3.4</td>
<td>1080 ± 23.0</td>
<td>1280 ± 35.8*</td>
<td>1450 ± 28.4***</td>
</tr>
<tr>
<td>sTNF-αRI, ng/mL</td>
<td>1.20 ± 0.60</td>
<td>2.08 ± 0.21***</td>
<td>2.14 ± 0.18</td>
<td>2.20 ± 0.19*</td>
</tr>
<tr>
<td>8-isoprostane, ng/mL</td>
<td>1.41 ± 0.25</td>
<td>9.17 ± 1.72**</td>
<td>19.30 ± 0.99***</td>
<td>14.90 ± 3.70***</td>
</tr>
<tr>
<td>CRP mg/L</td>
<td>6.25 ± 0.33</td>
<td>6.08 ± 0.65</td>
<td>6.28 ± 0.51</td>
<td>6.38 ± 0.59</td>
</tr>
</tbody>
</table>

Note: * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs control group; * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs patients with duration of hypertension ≤ 5 years; * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs patients with duration of hypertension > 5 years.

### Table 4

Dynamics of the cytokines, CRP and 8-isoprostane in the course of combined antihypertensive therapy in the observed patients (x ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I group</th>
<th>II group</th>
<th>III group</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α, pg/mL, prior to treatment</td>
<td>1150 ± 19.6</td>
<td>1330 ± 22.6</td>
<td>782 ± 23.7</td>
</tr>
<tr>
<td>sTNF-αRI, pg/mL, prior to treatment</td>
<td>44.8 ± 8.21***</td>
<td>45.0 ± 5.63***</td>
<td>40.6 ± 15.8***</td>
</tr>
<tr>
<td>8-isoprostane, pg/mL, prior to treatment</td>
<td>2.17 ± 0.12</td>
<td>2.10 ± 0.16</td>
<td>2.25 ± 0.21</td>
</tr>
<tr>
<td>CRP mg/L, prior to treatment</td>
<td>5.36 ± 17.4</td>
<td>6.33 ± 19.3</td>
<td>34.9 ± 12.2</td>
</tr>
<tr>
<td>8-isoprostane, pg/mL, after 2 months treatment</td>
<td>18.6 ± 7.8**</td>
<td>17.1 ± 6.4**</td>
<td>17.1 ± 6.6**</td>
</tr>
<tr>
<td>sTNF-αRI, pg/mL, after 4 months treatment</td>
<td>20.5 ± 17.4</td>
<td>12.7 ± 9.6</td>
<td>20.2 ± 11.9</td>
</tr>
<tr>
<td>TNF-α, pg/mL, after 2 months treatment</td>
<td>12.3 ± 7.27*</td>
<td>2.4 ± 1.5</td>
<td>10.2 ± 7.61*</td>
</tr>
<tr>
<td>CRP mg/L, after 2 months treatment</td>
<td>5.86 ± 0.48</td>
<td>6.81 ± 0.59</td>
<td>6.30 ± 0.49</td>
</tr>
<tr>
<td>8-isoprostane, pg/mL, after 2 months treatment</td>
<td>3.85 ± 0.36</td>
<td>3.68 ± 0.38*</td>
<td>5.14 ± 0.42</td>
</tr>
</tbody>
</table>

Note: * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs levels prior to treatment.

In the second group of patients, on the background of treatment with a combination of laclidipine and candesartan, the mean TNF-α levels decreased by 88 pg/mL (66.2%) compared to the baseline before treatment (Table 4). With respect to sTNF-αRI, the reverse trend was observed, that is, an increase in its mean level by 0.53 ng/mL (25.2%) after treatment. A 73.0% decrease in TNF-α/sTNF-αRI ratio reflected a significant decrease in the level of autoimmun activation under the influence of 10-week ARB + CCB therapy. In the third group of patients, the combination of fosinopril sodium with hydrochlorothiazide significantly reduced the mean TNF-α levels by 37.6 pg/mL (48.1%). With respect to sTNF-αRI, an insignificant increase in its mean level after treatment by 0.13 ng/mL (5.8%) was observed. The value of TNF-α/sTNF-αRI ratio decreased by 17.7 (by 50.9%), compared to baseline before treatment, which also reflects a decrease in the level of autoimmune activation under the influence of therapy.

Analyzing the obtained data with respect to the level of 8-isoprostane r two months from the start of therapy on the background of treatment, in the third group patients, its level decreased by 50% (2-fold) from the initial level. In the second group of patients, the reduction in serum levels of 8-isoprostane by 80.9% (5.2-fold) was observed after 2 months of treatment compared with the baseline. In the first group of patients, the levels of 8-isoprostane also decreased by 40% (1.7-fold) from the initial level after

two months of therapy. Thus, different protocols of combined therapy with beta-blocker plus diuretic (bisoprolol and indapamide) and ACE inhibitor plus diuretic (fosinopril and hydrochlorothiazide) expressed a similar effect on the dynamics of 8-isoprostane levels during two months of treatment. Analyzing the dynamics of CRP on the background of combined treatment, we obtained the following data: the mean values of serum CRP had decreased by 2.01 mg/L (34.3%), by 3.13 mg/L (46.0%) by 1.16 mg/L (18.4%) in the L I and III clinical groups, respectively. Under the influence of combined antihypertensive therapy with all three schemes, there was an improvement in clinical status, expressed by a decrease in the intensity and frequency of headaches, dizziness, pain in the heart area, fatigue, and an increase in exercise tolerance as a result of significant reduction in blood pressure (Table 5). All patients who received treatment with one of the combined anti-hypertensive therapy regimens were discharged from the hospital (on the 10–14th day of treatment) in a satisfactory condition.

Table 5
Blood pressure and heart rate dynamics during the course of treatment (x ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I group</th>
<th>II group</th>
<th>III group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure prior to treatment</td>
<td>168.3 ± 26.6</td>
<td>176.0 ± 27.2</td>
<td>180.2 ± 28.6</td>
</tr>
<tr>
<td>Systolic blood pressure after 2 weeks of treatment</td>
<td>129.5 ± 11.9***</td>
<td>131.6 ± 11.0***</td>
<td>132.6 ± 9.7***</td>
</tr>
<tr>
<td>Diastolic blood pressure prior to treatment</td>
<td>100.8 ± 12.7</td>
<td>105.2 ± 14.1</td>
<td>107.1 ± 11.3</td>
</tr>
<tr>
<td>Diastolic blood pressure after 2 weeks of treatment</td>
<td>75.5 ± 6.3***</td>
<td>75.3 ± 5.0***</td>
<td>76.5 ± 5.8***</td>
</tr>
<tr>
<td>Average BP blood pressure prior to treatment</td>
<td>123.3 ± 16.0</td>
<td>128.6 ± 17.6</td>
<td>131.3 ± 15.7</td>
</tr>
<tr>
<td>Average BP blood pressure after 2 weeks of treatment</td>
<td>93.4 ± 6.5***</td>
<td>93.9 ± 6.2***</td>
<td>95.0 ± 5.7***</td>
</tr>
<tr>
<td>Pulse blood pressure prior to treatment</td>
<td>67.5 ± 19.9</td>
<td>71.2 ± 18.0</td>
<td>73.1 ± 22.2</td>
</tr>
<tr>
<td>Pulse blood pressure after 2 weeks of treatment</td>
<td>54.0 ± 11.8***</td>
<td>55.9 ± 10.6***</td>
<td>55.6 ± 10.1***</td>
</tr>
<tr>
<td>HR prior to treatment</td>
<td>83.4 ± 11.9</td>
<td>74.2 ± 9.2</td>
<td>78.4 ± 12.1</td>
</tr>
<tr>
<td>HR after 2 weeks of treatment</td>
<td>75.3 ± 6.2*</td>
<td>76.7 ± 4.8</td>
<td>73.1 ± 6.6*</td>
</tr>
</tbody>
</table>

Note: * – P < 0.05; ** – P < 0.01; *** – P < 0.001; vs levels prior to treatment.

In patients treated with bisoprolol and indapamide, a reduction in the mean values of office systolic blood pressure (SBP) by 38.8 mm Hg, office diastolic blood pressure (DBP) by 25.3 mm Hg, average BP by 29.8 mm Hg, pulse BP by 13.5 mm Hg during the period of inpatient treatment was observed (23.1%, 25.1%, 24.2%, and 20.0%, respectively). A decrease in the intensity and frequency of headaches, dizziness, pain in the heart area, fatigue, and an increase in exercise tolerance as a result of significant reduction in blood pressure (Table 5). All patients who received candesartan and lacidipine, there were similar changes during the inpatient treatment in the mean values of the office SBP by 44.5 mm Hg, office DBP 29.9 mm Hg, mean BP by 34.8 mm Hg, pulse BP by 15.2 mm Hg (25.3%, 28.4%, 27.6%, and 24.0%, respectively vs levels prior to treatment).

The mean value of TNF-α was 14.2 times higher compared to control values, suggesting the possible role of hemodynamic stress as one of the stimuli for increasing synthesis and release of pro-inflammatory cytokines, in particular TNF-α, into the circulation (Grannder, 2004; Azra & Feel, 2005; Bautista et al., 2005). The mean value of sTNF-αR1 in patients with increased TNF-α activity (likely, due to increased blood pressure) was 1.78 times, or 78.3% higher, compared to normal subjects.

Numerous epidemiological studies have shown a relationship between tachycardia and hypertension. Increased heart rate is associated with many risk factors, including dyslipidemia, hyperinsulinemia, obesity, and elevated hemocrit. Tachycardia is a marker of increased activity of the sympathetic nervous system. It is known that a decrease in heart rate correlates with longer life in mammals. Moreover, ß-blockers affect the renin-angiotensin-aldosterone system (RAAS), inhibiting the release of renin by the kidneys with urine, the rest (46.0%) – by hepatic degradation of active metabolites with their sequential release through the gastrointestinal tract. It is important to note that the decrease in renal filtration increases...
proportionally the hepatic route of excretion of the drug, and on the contrary, in liver disease – increases the contribution of renal excretion. Actually, this pharmacokinetic feature of fosinopril is the basis of the important clinical recommendations: no additional correction of fosinopril doses is usually required in renal and hepatic failure (Ageev & Mareev, 2000; Karpov, 2001). This characteristic feature of fosinopril makes it a safer choice than other ACEIs for heart failure patients with impaired kidney function resulting from impaired renal perfusion as fosinopril can still be eliminated by the liver, preventing excessive increase of its serum levels.

The results of the current study allow us to suggest that in individuals with grade 1 hypertension, increase of sTNF-aR1 (2.02 ± 0.22 ng/mL) at high levels of the circulating TNF-α (112 ± 26 ng/mL) can possibly be regarded as an adaptive mechanism that, on one hand, reduces the number of active receptors on the surface of target cells, and on the other hand, may neutralize the bioactivity of TNF-α through the soluble receptor forms (sTNF-aR1) binding with the latter. In patients with grade 2 hypertension, a parallel increase in sTNF-aR1 (2.13 ± 0.16 ng/mL) was probably not enough to neutralize the negative effect of TNF-α (142 ± 27 ng/mL), as could be evidenced by a further increase in the TNF-α/sTNF-aR1 ratio (66.7 ± 55.4 in grade 1 hypertension and 11.0 in normotensive individuals). At the maximal levels of blood pressure the levels of TNF-α were decreasing (117 ± 19 ng/mL), which possibly could be due to its binding to sTNF-aR1. On the other hand, we can suggest the possibility of TNF-α triggering a cascade leading to apoptosis of cells producing cytokine. The further increase in sTNF-aR1 on the background of a decrease in TNF-α has a positive significance. The fact that the TNF-α/sTNF-aR1 ratio value was 53.4, with the TNF-α levels also still exceeding those in grade 1 hypertension and healthy individuals, could indicate that such a level of sTNF-aR1 is unable to inactivate TNF-α cytotoxicity.

According to the single-factor dispersion analysis, there was an increase in the CRP serum levels in patients with hypertension. This increase depended only on the duration of hypertension, but not on the grade of BP elevation; there was also no significant correlation between CRP and BP, possibly being consistent with existing data on the definition of CRP as an independent risk factor for hypertension. In particular, an increased level of CRP had been shown in normotensive individuals who later developed essential hypertension. The increased level of CRP is related to the deterioration of endothelium-dependent relaxation, posing a potential risk of developing hypertension. In the hypertensive population, it is established that CRP is an independent predictor of atherosclerosis progression, more significant than pulse and systolic blood pressure. Our findings suggest that elevated CRP levels can be considered as a marker of systemic inflammation in hypertensive patients (Bautista, 2001; Orat et al., 2008).

Taking into account the correlations revealed, it can indicate the role of OS in the pathogenesis of hypertension as a damaging mechanism that promotes the activation of immune mechanisms, nonspecific inflammation and the further progression of the disease. OS causes damage to the vascular endothelium, and the main disorders in the vascular wall that are characteristic for hypertension are endothelial dysfunction and hypertrophy of the smooth muscle cells.

Conclusions

The data obtained in the course of two months treatment testifies to the anti-inflammatory and anti-apolipotic effects of the combined antihypertensive therapy. The most pronounced result was observed in individuals receiving combined therapy with lucidipine plus candesartan and bisoprolol plus indapamide.

It is important that further studies are made to assess the activity of proinflammatory cytokines, namely tumour necrosis factor-α and its type I soluble receptor, levels of C-reactive protein as an independent marker of systemic inflammation, levels of 8-iso-prostaglandin as a marker of oxidative stress, involving larger study populations with long follow-up periods. The results of advanced research will help in the formation of pathogenetically justified and prognostically significant antihypertensive therapy regimens.

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