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Short-term antihypertensive therapy lowers the C-reactive protein level

Krótkotrwałe leczenie przeciwnadciśnieniowe zmniejsza stężenie białka C-reaktywnego

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: There is a growing body of data concerning significant interactions between markers of inflammation and cardiovascular diseases such as hypertension accompanied by elevated levels of plasma C-reactive protein (CRP). Therefore CRP is thought to be an independent risk factor of cardiovascular diseases.

Material/Methods: The aim of this study was to evaluate the effects of antihypertensive therapy (perindopril, bisoprolol and combined therapy) on plasma CRP concentration in 67 subjects with mild or moderate hypertension who have been treatment-naive and otherwise healthy.

Results: The results show a correlation between CRP level and blood pressure values. BP reduction was associated with a decrease in CRP concentration. The CRP-lowering effect of perindopril and bisoprolol was comparable and the degree of reduction might reflect their similar influence on blood pressure. Combined treatment influenced the CRP level to a greater extent than both monotherapies.

Conclusions: Plasma CRP level was lowered by antihypertensive therapy independently of the drug applied. The CRP level did not normalize completely in moderate hypertensive patients.

Key words: **antihypertensive therapy • C-reactive protein • perindopril • bisoprolol**

Streszczenie

Wstęp: Wyniki wielu ostatnio opublikowanych badań ukazują istotne związki między wskaźnikami stanu zapalnego a chorobami układu sercowo-naczyniowego. Stężenie CRP jest uważane za niezależny czynnik ryzyka rozwoju chorób układu krążenia i jest ono zwiększone między innymi u chorych na nadciśnienie tętnicze.

Materiał/Metody: Celem badania była ocena wpływu leczenia obniżającego ciśnienie tętnicze (za pomocą perindoprilu, bisoprololu i leczenia skojarzonego) na stężenie CRP w osoczu chorych na nadciśnienie tętnicze łagodne i umiarkowane.

Wyniki: Zaobserwowano korelację między stężeniem CRP a wartościami ciśnienia tętniczego. Terapia przeciwnadciśnieniowa doprowadziła do zmniejszenia stężenia CRP. Leczenie bisoprololem i perindoprilem spowodowało porównywalne zmniejszenie stężenia CRP, co prawdopodobnie odzwierciedla podobny efekt hipotensyjny obu leków. Leczenie skojarzone bardziej niż każda z monoterapii zmniejszało stężenie CRP.

Wnioski: W trakcie stosowania każdej z terapii przeciwnadciśnieniowych stwierdzono zmniejszenie stężenia CRP. U chorych na umiarkowane nadciśnienie tętnicze nie uzyskano jednak normalizacji stężenia CRP.

Słowa kluczowe: **leczenie nadciśnienia • białko C-reaktywne • perindopril • bisoprolol**

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Abbreviations: **ACE-I** – angiotensin-converting enzyme inhibitor; **ACS** – acute coronary syndrome; **ANOVA** – analysis of variance; **AT-1** – angiotensin receptor 1; **BMI** – body mass index; **BP** – blood pressure; **BPM** – blood pressure monitor; **CRP** – C-reactive protein; **ELISA** – enzyme-linked immunosorbent assay; **ESC/ESH** – European Society of Cardiology/European Society of Hypertension; **ICAM-1** – intercellular adhesion molecule 1; **HDL** – high-density lipoprotein; **IL** – interleukin; **LDL** – low-density lipoprotein; **MCP-1** – monocyte chemoattractant protein-1; **NF-κB** – nuclear factor kappa B; **NOS** – NO synthase; **PAI-1** – plasminogen activator inhibitor 1; **RAS** – renin-angiotensin system; **TG** – triglycerides; **TNF** – tumor necrosis factor; **VCAM-1** – vascular cell adhesion molecule 1.

Introduction

There is a growing body of data concerning significant interactions between markers of inflammation and cardiovascular diseases. Diseases linked to atherosclerosis, such as myocardial infarction, stroke or unstable angina, are characterized by an increase in inflammatory markers, including plasma C-reactive protein (CRP). Hypertension is accompanied by an elevated level of CRP and other proinflammatory cytokines together with adhesive molecules [2,3,4,31,35].

The Women's Health Study (WHS), performed on 20,250 women with high-normal blood pressure, confirmed a significant association between the serum CRP level and the risk of subsequent hypertension development [33]. Convergent results were described by Niskanen et al. [25]. It has been shown that increased CRP level (>3 mg/L) in comparison with lower values (<1 mg/L) was associated with more frequent occurrence of hypertension. In 2004, the results of the ATTICA study (with 3,000 subjects) disclosed that patients prone to hypertension had augmented immune system reactivity that was expressed, inter alia, by increased (30%) levels of CRP (3). However, to date, there are still only a few studies concerning the influence of modern antihypertensive therapy on CRP level [9,34,41]. A question asked was whether long-lasting cardioselective beta-adrenolytics were able to affect CRP level with effectiveness comparable to ACE-I. Additionally, we sought to evaluate the magnitude of the influence of combined therapy (with bisoprolol and perindopril) on blood pressure and CRP level in patients with moderate hypertension. The uniqueness of our study lies in the strict inclusion criteria concerning patients with a normal level of lipids (the mean values of lipids were as follows: total cholesterol [TC] 5.11 mmol/L, high density cholesterol [HDL] 1.25 mmol/L, low density cholesterol [LDL] 3.28 mmol/L, triglycerides [TG] 1.5 mmol/L). None of the studies performed so far have referred to total cholesterol level, though its positive correlation with plasma CRP concentration has been shown.

Unlike in similar studies, the method of 24-hour blood pressure monitoring was used to assess blood pressure. There is only a single study reported to use this kind of BP appraisal [28]. Additionally, to date, there have been no studies considering the influence of long-lasting cardioselective beta-blockers on CRP level. The studies published to date have provided an insight into the effects of non-cardioselective beta-blockers such as propranolol and carvedilol [24] or short-acting metoprolol [18]. Our study presents the influence of bisoprolol as a long-lasting, cardioselective beta-blocker, perindopril as a modern ACE-I, and combined therapy on blood pressure and CRP level.

Material and Methods

Study population

The study was carried out on 67 subjects divided into 3 groups (Table 1). The first group included 22 patients with 2nd stage (moderate) hypertension, while the second and third covered patients with 1st stage (mild) arterial hypertension. The control group consisted of 30 normotensive patients.

Hypertension had been recently diagnosed in all subjects, none of whom had ever been treated with any antihypertensive drugs. Patients were considered hypertensive if

Table 1. Patients characteristics

Parameters	Control group	Study groups		
Number of patients	30	67		
		22	22	23
Hypertension	N/A	Moderate	Mild	Mild
Male/Female	17/13	12/10	12/10	12/11
Mean BMI (kg/m^2)	25.5±2.2	25.5±2.5	25.6±2.1	25.0±3.1
Mean age (years)	43.6±9.2	45.7±8.2	44.1±8.2	46.2±11.7
Perindopril	N/A	22	22	N/A
Bisoprolol	N/A	22	N/A	23

they presented blood pressure higher than 140/90 mmHg following at least four sets of readings (taken at week intervals) and having injuries of retinal arteries corresponding to 1st or 2nd stage arterial hypertension on fundoscopy. Additionally, 24-hour ambulatory non-invasive blood pressure monitoring was performed before and after 1-month therapy in each patient. Control subjects had a supine systolic blood pressure lower than 130 mmHg and a diastolic one lower than 85 mmHg. The moderate hypertension group was given combined therapy (perindopril 4 mg daily plus bisoprolol 5 mg daily, both administered once a day in the morning). Patients with mild hypertension were randomized into two groups: those taking perindopril (4 mg once a day in the morning) and those taking bisoprolol (5 mg in the morning). All patients signed the informed consent.

Exclusion criteria included alcohol or drug abuse, presence of secondary hypertension, isolated systolic or 3rd stage hypertension, kidney, heart, liver or gastrointestinal diseases, inflammatory diseases, diabetes mellitus and lipid disorders. Patients treated with any drugs influencing blood pressure or with an acute or chronic inflammatory state were excluded as well as those with endocrine, neurological, haematological and metabolic disturbances or cancer history. The study population was comparable in gender, age, body mass index, lipid level and smoking history. Subjects with acute or chronic inflammation were excluded on the basis of the physical examination and basic laboratory tests (complete blood count, CRP, electrolytes, transaminases, glucose, creatinine and urinalysis). When it was necessary, additional laboratory tests were conducted (electrophoresis, oral glucose tolerance test) together with the radiographic examination (chest and dental x-rays) and the consultation of specialists (such as an otolaryngologist). Each patient underwent Doppler ultrasound imaging of the renal arteries.

Laboratory assays

A heparin blood sample (5 ml) was collected between 800 and 900 a.m. to avoid circadian fluctuations of the parameters studied following the Mobil-Graph Units for non-invasive 24-hour blood pressure monitoring.

The CRP level in plasma was assessed with enzyme-linked immunosorbent assay (ELISA) using MP Biomedicals' High Sensitivity C-Reactive Protein Enzyme Immunoassay Test Kit according to the manufacturer's instructions. All of the mentioned parameters were analyzed before and after four weeks of treatment.

Statistics

Results were expressed as the mean +/–SD. The normality of distribution was checked by means of the Kolmogorov-Smirnov test. The statistical evaluation was performed using analysis of variance (ANOVA) and post hoc comparison was conducted by means of the Newman-Keuls test. In the case of non-normally distributed data, statistical evaluation was performed by Kruskal-Wallis and Dunn's tests. Comparison of parameters before and after therapy in the same group was investigated with the Wilcoxon test. The correlation between CRP level and systolic and diastolic blood pressure was calculated using Spearman's method. All statistical analyses were conducted using Graph Pad Prism 4.0 and Statistica 6.0. A p-value of <0.05 was considered significant.

Institutional Review Board

The Local Review Board (Medical University of Silesia, Katowice, Poland) accepted the study protocol.

Results

Drug therapies were not associated with any serious adverse effects. Two patients treated with perindopril (one with mild hypertension, another with moderate hypertension) reported cough at the end of the study period. In the bisoprolol-treated group two patients suffered from fatigue and one from bradycardia (<50 bpm during the day). All patients, excluding those mentioned above, continued the treatment after the end of the study period.

24 h blood pressure monitoring

The measurements were taken and evaluated according to the ESC-ESH guidelines (2007). In the group with moderate hypertension the four-week combined therapy resulted in a decrease of all measured blood pressure parameters, both systolic and diastolic (Table 2).

There was no alteration in the ratio between day and night pressure drop. Blood pressure values in mild hypertensive

Table 2. Values of blood pressure before and after therapy

Treatment		Hypertension stage 2		Hypertension stage 1			
		Perindopril + bisoprolol		Perindopril		Bisoprolol	
		Before	After	Before	After	Before	After
Mean 24-hour systolic pressure/mmHg/	Mean+/–SD	144.3±5.1	119.4±8.3*	137.4±13.4	121.6±10.0**	136.7±10.4	124.6±9.0**
Mean 24-hour diastolic pressure/mmHg/	Mean+/–SD	90.2±3.2	73.9±5.8*	86.3±10.1	78.3±6.1***	82.7±5.9	78.6±5.3**
Mean day systolic pressure/mmHg/	Mean+/–SD	149.7±5.2	122.8±7.9*	145.0±13.4	124.9±10.1*	141.5±11.4	130.1±11.3**
Mean day diastolic pressure/mmHg/	Mean+/–SD	93.5±3.7	76.4±5.1*	90.6±10.4	79.8±6.6*	86.4±6.8	82.8±6.0***
Dipper (drop percentage day/night)	Mean+/–SD	10.2±5.6	11.7±7.4	16.3±7.7	9.7±7.5	11.8±6.1	10.5±4.5

* p<0.001, ** p<0.01, *** p<0.05.

Table 3. The CRP level (mg/L) in the control and study groups

Parameters	Control group	Study groups		
Hypertension	N/A	Moderate (combined therapy)	Mild (bisoprolol)	Mild (perindopril)
CRP before therapy	1.42±0.85	2.55±1.28	2.04±1.36	1.99±1.3
CRP after therapy	N/A	1.84±1.3	1.35±0.92	1.56±1.29
p (before *vs.* after)	N/A	0.03	0.001	ns
p (after *vs.* control group)	N/A	0.001	ns	ns
p (before *vs.* control)	N/A	<0.001	ns	ns

patients were significantly lower than in the group of moderate hypertension, but still met all criteria of ESC-ESH. Beta-blocker therapy resulted in significantly lower mean blood pressures (diastolic and systolic pressure) during a twenty-four-hour period as well as during waking hours. The decrease in night values (diastolic and systolic) was not significant. Corresponding results were noted in an ACE inhibitor treated group. Both hypertension therapies were similarly effective, except for the considerably greater reduction of mean diastolic pressure during the day period by perindopril (79.8 *vs.* 82.8 mmHg; p=0.017).

Plasma CRP level

The baseline CRP level correlated with the increase of blood pressure in a linear manner. At the beginning of the study the level of CRP did not statistically differ between control subjects and patients with mild hypertension. In patients with moderate hypertension the difference reached statistical significance in relation to the control group (p<0.001) as well as to the mild hypertension group (p<0.04) (Table 3).

Following the antihypertensive therapy, a progressive reduction in CRP level was observed. In patients with moderate hypertension the decrease reached 28% (p=0.03) but even then it was higher than in control subjects. The bisoprolol treatment was associated with a CRP decrease reaching 35% (p<0.001) while the perindopril therapy decreased it insignificantly by 22% (Table 3).

The comparison of both groups with mild hypertension did not reveal any differences in initial plasma CRP level (p=0.91). The extent of CRP level reduction in the perindopril-treated group was analogous to the bisoprolol-treated group.

Table 4. Correlation coefficients for CRP and systolic pressure

CRP	Mean day systolic pressure	Mean night systolic pressure	Mean 24-hour systolic pressure
r	0.25	0.254	0.32
p	0.077	0.075	0.02

Correlation analysis

Correlation analysis revealed an association between initial CRP level and the mean 24-hour systolic blood pressure (r=0.32, p=0.02) (Table 4).

Correlation coefficients for mean day and night systolic pressure with CRP level did not reach statistical significance.

Discussion

The obtained results revealed that hypertension is associated with the intensified function of the immune system, corresponding to an increased CRP level. Our study compared head-to-head effects of monotherapies with perindopril and bisoprolol as well as combined therapy. We observed similar effects on blood pressure associated with monotherapies and superior efficiency of combined therapy. The CRP level is thought to be an independent factor of increased mortality. The JUPITER study showed that mortality may be reduced by treatment with agents (statins) reducing the CRP level [29]. We noted that an increase of blood pressure is accompanied by an elevated CRP level. During the treatment significant reductions of CRP level were observed. Nevertheless, the CRP level did not drop after 30 days of therapy to the level seen in healthy subjects.

In the past few years the significant role of CRP in atherosclerosis has been confirmed. CRP increases the expression of adhesive molecules and chemokines on endothelial cells [27] as well as LDL uptake by macrophages [14,15,42], not to mention the raising of the AT-1 receptor expression on smooth muscle cells [40]. Furthermore, CRP inhibits nitric oxide synthase (NOS), and increases release of endothelin-1, resulting in endothelium dysfunction [38,39]. In those cases the CRP acts mainly through a specific Fc-gamma receptor, leading to a decrease in NOS activity and prostacyclin levels and an augmented expression of adhesion molecules (e.g. ICAM-1 and VCAM-1) [10].

The increased level of CRP correlates with myocardial infarction severity and its complications [1] together with endothelial cell dysfunction and the risk of acute coronary syndromes (ACS) in patients with stable angina [12,13,16] as well as in patients with ACS without ST-elevation [23]. The assessment of CRP level in patients with stable angina is recommended by the American Heart Association guidelines for cardiac risk evaluation. There are three ranges (<1.0, 1.0–3.0 and >3.0 mg/L) that correspond to three risk categories: low, moderate and high [26].

The relation has also been confirmed in patients at risk of hypertension. A linear correlation was observed during eight-year follow-up in the WHS study between CRP level and the risk of hypertension development in the future. The level of CRP was 30% higher in patients with high-normal blood pressure compared to healthy subjects [6]. The level of CRP ≥3.0 mg/L increased the risk of hypertension development three-fold. Another study showed that a CRP level ≥3.0 mg/L increased the risk of hypertension by 79% only when coexisting with an increased body mass index (BMI) [19].

In our study, the level of CRP increased linearly with the BP. Those results appertain to the observations of Sesso et al. [31] along with the findings of Schillaci et al. [33] that revealed a correlation of CRP level with systolic values acquired during 24-hour blood pressure monitoring ($r=0.28$, $p<0.001$). No correlation was observed with diastolic pressure values.

Following one month of antihypertensive therapy, the previously increased CRP levels in the mild hypertension groups (1.45 mg/L) had normalized. The CRP level in the moderate hypertension group had decreased, but still remained 23% higher than in control subjects (1.84 *vs.* 1.42 mg/L). The normalization of CRP appears to have been related to a decrease in BP.

There are only a few studies assessing the effects of antihypertensive therapy with cardioselective beta-blockers on CRP in normolipidemic subjects. Yasunari et al. [41] reported the effect of six-month therapy with propranolol versus carvedilol on CRP level. The former did not lower the CRP level but the latter reduced it by 78%. King et al. [18] demonstrated the CRP-lowering properties of metoprolol in 75 hypertensive patients. The level of CRP was decreased after one-month therapy, while another 2 months of therapy brought no further reduction. Recently, two studies have corroborated the reduction in CRP level during treatment with drugs affecting the renin-angiotensin system (RAS). Nevertheless, there are also studies that have shown no effects on CRP level by antihypertensive treatment [22].

We did not observe a significant difference in the level of CRP between the bisoprolol group (1.35 mg/L) and the perindopril group (1.56 mg/L) at the end of the study. However, the magnitude of reduction was significantly greater after beta-blocker treatment. The positive effects of beta-blockers have been observed by others, including in patients with angina pectoris (CRP level =1.8 mg/L in beta-blocker treated group *vs.* 3.1 mg/L in other therapies) as well as in patients with heart failure (the CRP level was 37% lower in the beta-blocker group) [20].

The proinflammatory properties of angiotensin-2 result from the stimulation of AT-1 receptors that lead to the secondary activation of nuclear factor kappa B (NF-κB) and synthesis of cytokines (MCP-1, Il-6, TNF-alpha, Il-1, PAI-1) in inflammatory, endothelial and vascular smooth muscle cells (4, 14, 17, 37–39). The angiotensin-2 augments the phospholipase C activation, leading to a higher intracellular calcium level and endothelin-1 release [5].

Considering all of these facts, the angiotensin-converting enzyme inhibitors are believed to lower the CRP level in hypertension. The study by Mitrovic et al. [22] demonstrated a decrease in CRP level after 3-month therapy with ramipril in patients with atherosclerosis. Also in the MESA study [26] this beneficial effect was observed, while the Trandolapril Cardiac Evaluation (TRACE) study found no influence on CRP level in patients with myocardial infarction [7]. Similarly, enalapril did not affect the CRP level in patients with angina pectoris or after an acute coronary episode [30,37]. Monotherapy with ramipril reduced the CRP level in diabetic (by 24%) and atherosclerotic (by 32%) patients [22] but no effect in diabetic and hypertensive patients was observed after treatment with lisinopril [32]. The prospective multi-center study by Di Napoli and Papa [11] showed that treatment with ACE-I lowered the CRP level 2.6-fold and reduced the risk of recurrent cerebral stroke.

One of the limitations of our study was the relatively small sample size due to strict inclusion criteria. However, as a result a high degree of homogeneity in treated groups was obtained.

In conclusion, our results suggest that the level of CRP at least partly depends on blood pressure values. A linear correlation between CRP and blood pressure was revealed. Reduction in blood pressure values after antihypertensive therapy and the lack of statistical differences between perindopril and bisoprolol treated groups might suggest that the CRP-lowering effect of those medications depends on their influence on blood pressure. The blood pressure normalization is followed by a decrease of CRP level, which might in turn be reflected in better cardiovascular outcome in the future (Table 5).

Table 5. Summary of the study

What is known about topic	What this study adds
• Hypertension is accompanied by an increased CRP level • Elevated CRP level is a known cardiovascular risk factor • Antihypertensive therapies reduce CRP level	• A head-to-head comparison of the effects of a selective beta blocker (bisoprolol) vs. a commonly used ACE-I (perindopril) • Beneficial effects of the combined therapy compared to monotherapies (but not normalization of CRP)

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