Correction of Endothelial Dysfunction in Patients with Arterial Hypertension

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We examined 38 patients (mean age 55.92±1.56 years) with a 3-5-year history of arterial hypertension. The study showed that hypertension is accompanied by endothelial dysfunction and one of its forming factors is activation of the inflammatory response. Highly sensitive diagnostic tests can verify initiation of inflammation in preclinical manifestations. The use of nonsteroidal anti-inflammatory drugs, irrespective of the tropism to cyclooxygenase forms, alleviates manifestations of endothelial dysfunction in patients with arterial hypertension.

Key Words: *hypertension; endothelial dysfunction; inflammation; cyclooxygenase-1, -2;, non-steroidal anti-inflammatory drugs*

Studies in recent decades have convincingly proved that endothelial dysfunction plays a key role in the development and progression of cardiovascular diseases, *e.g.* arterial hypertension (AH). In this case, activation of the proinflammatory potential of the vascular wall is one of the major factors of its development [1,6]. Clinical guidelines and protocols for patients with AH do not include correction of this factor of pathogenesis. At the same time, some antihypertensive drugs correct endothelial dysfunction via other mechanisms [2,5,9]. In light of this it is interesting to study the possibility of using other drugs, *e.g.* nonsteroidal anti-inflammatory drugs suppressing inflammation by blocking cyclooxygenase, for this purpose. Two cyclooxygenase isoforms (cyclooxygenase-1 and -2) differ in selectivity and pharmacodynamics. Cyclooxygenase-1 (COX-1) is involved in various physiological processes and its blockade produces mainly antiplatelet effect. Cyclooxygenase-2 (COX-2) is secreted in some pathological reactions including inflammation. Its suppression inhibits these reactions and has virtually no effect on hemostasis system [4,7].

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Here we studied the possibility of using nonsteroidal anti-inflammatory drugs for correction of endothelial dysfunction in patients with AH.

MATERIALS AND METHODS

The study involved 38 patients (mean age 55.92±1.56 years). The main criterion for inclusion in the study was a 3-5-year history of AH provided that the target blood pressure values were achieved at the previous stages of therapy. The diagnosis was verified on the basis of history, physical examination by cardiologist, electrocardiogram, causal blood pressure measurements, and laboratory tests. All patients included in the study received standard antihypertensive mono- or combined therapy [4,8]. After completion of diagnostic testing specified in a study protocol, the patients were divided into two groups. In group 1, antihypertensive therapy was supplemented with COX-1 blocker acetylsalicylic acid (ASA) in a dose of 150 mg (Cardiomagnyl, Nycomed Danmark, ApS) once a day. COX-2 inhibitor celecoxib (Celebrex, SEARLE division of Monsanto pls) was administered to group 2 patients in a daily dose of 200 mg. Period of follow-up with active therapeutic intervention was 2 weeks.

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The intensity of the inflammatory response was evaluated by the levels of inflammatory markers in the blood: intercellular adhesion molecule-1 (sICAM-1) and C-reactive protein (CRP) were measured by a highly sensitive enzyme immunoassay using Bender Medsystems reagents on a Stat Fax 2100 reader (Awareness technology Inc.) and Plate Stat software.

Endothelial function was evaluated by a noninvasive method measuring flow-induced endothelium-dependent vasodilation (EDVD) using high-resolution ultrasound developed by D. Celermajer *et al*. [10,11] in the modification of Y. Hirooka *et al*. [12] and O. V. Ivanova *et al.* [3] on a Philips En Visor C device.

The data were processed using methods of variation statistics. Quantitative data were expressed as mean±standard error of the mean. In all statistical tests, differences were significant at $p<0.05$. For ordinal variables, intra- and intergroup differences were evaluated by nonparametric tests, *i.e.* Wilcoxon rank test for paired cases and Mann–Whitney *U* test. For qualitative variables, Fisher's angular transformation was used.

RESULTS

Endothelial damage caused by factors accompanying AH followed by activation of the inflammatory process, oxidative stress, and prothrombotic shift contributed to inadequate production of vasoactive substances and shifted the balance in the systems of vascular tone modulation towards vasoconstriction maintaining high blood pressure and worsening manifestations of endothelial dysfunction.

First, we should pay attention to the presence of endothelial dysfunction detectable by ultrasonography in 100% examined patients, even when the target blood pressure was achieved. In this case, the estimated levels of EDVD (by the results of a blind randomization in study groups) did not differ significantly, but were lower in patients treated with celecoxib (Table 1).

The used treatment options provided positive dynamics of EDVD parameters. In the group of patients treated with ASA, the coefficient tended to increase and to day 14 of therapy was 9.37±1.77%, which is 28.3% higher than baseline (7.30±1.87%; $p>0.05$). By the end of observation period, the mean values of EDVD in patients receiving celecoxib also surpassed the baseline by 28.9% (6.42±1.03% *vs.* 4.98±1.15 initially; $p>0.05$). This fact indicates that even 2-week course of anti-inflammatory drugs helps to reduce the manifestations of endothelial dysfunction.

In parallel with the parameters of EDVD, we evaluated the severity of vascular endothelial damage by the level of sICAM-1. This marker was elevated in patients enrolled in the study, as well as the concentration of CRP, the main marker of the initiation of the inflammation cascade. The used variants of therapy showed positive effects with regard to several characteristics of endothelial dysfunction. Serum levels of sICAM decreased in 50% patients receiving celecoxib. After 2 weeks of therapy, the mean concentration of molecules was by 38.1% below the initial values ($p>0.05$; Table 1). Similar dynamics was noted after ASA therapy: 252.81±8.02 and 240.88±9.93 before and 2 weeks after therapy, respectively. CRP concentration underwent similar changes: it decreased by 42.3% ($p<0.05$) during celecoxib therapy (to 305.83±42.34 ng/ml by the end of the observation period *vs.* 417.08±46.71 ng/ml at baseline). Similar dynamics was obaerved against the background of ASA therapy: by day 14 CRP concentration decreased by 32.29% (to 237.88±26.80 ng/ml) compared to initial value (350.00±41.48 ng/ml).

Thus, AH is accompanied by endothelial dysfunction and one of its forming factors is activation of the inflammatory response. Highly sensitive diagnostic tests can verify initiation of inflammation at the preclinical stages. The use of non-steroidal anti-inflammatory drugs, irrespective of their tropism to cyclooxygenase forms, alleviates the manifestations of endothelial dysfunction in hypertensive patients,

TABLE 1. Changes in EDVD and Concentration of Inflammatory Markers against the Background of Complex Treatment of Hypertensive Patients with Non-Steroidal Anti-Inflammatory Drugs (*X±m*)

Parameter	Normal	ASA		Celecoxib	
		before treatment	after treatment	before treatment	after treatment
Soluble intercellular adhesion molecule-1, ng/ml	130-297	252.81±8.02	240.88±9.93	373.00±39.59	270.83±21.85
C-reactive protein, ng /ml	50-140	350.00±41.48	237.88±26.80*	530.08±46.71	305.83±42.34*
EDVD, %	8-13	7.30±1.87	9.37±1.77	4.98±1.15	6.42±1.03

Note: *$p<0.05$ compared to the parameter before treatment.

while maintaining and even increasing the gradient of coupling with characteristics of the inflammatory process.

REFERENCES

1. Y. I. Golovchenko and M. A. Treschinskaya, *Consilium Medicum*, **2**, No. 11, 38-40 (2008).
2. N. Sh. Zagidullin, K. F. Valeeva, and N. Hassanov, *Kardiologiya*, No. 5, 54-60 (2010).
3. O. V. Ivanova, T. V. Balakhonova, G. N. Soboleva, *et al., Kardiologiya*, **37**, No. 7, 41-45 (1997).
4. A. O. Conrady, *Arterial'naya Gipertensiya*, No. 1, 46-49 (2009).
5. V. I. Makolkin, *Rus. Med. Zh.*, No. 16, 1238-1241 (2007).
6. B. A. Namakanov and M. M. Rasulov, *Kardiovask. Ter. Prof.*, No. 4, Part II, 98-101 (2005).
7. E. L. Nasonov, *Serdtse*, **3**, No. 4, 209-212 (2004).
8. I. E. Chazova and L. G. Ratova, *Serdtse*, **4**, No. 3, 120-126 (2005).
9. T. K. Chernyavskaya, *Kardiologiya. Atmosfera*, No. 2, 21-27 (2005).
10. D. S. Celermajer, K. E. Sorensen, D. J. Spiegelhalter, *et al., J. Am. Coll. Cardiol.*, **24**, No. 2, 471-476 (1994).
11. D. S. Celermajer, K. E. Sorensen, V. M. Gooch, *et al*., *Lancet*, **340**, 1111-1115 (1992).
12. Y. Hirooka, K. Egashira, T. Imaizumi, *et al., J. Am. Coll. Cardiol.*, **24**, No. 4, 948-955 (1994).