Use of Impaza in the Treatment of Erectile Dysfunction in Patients with Essential Hypertension and CHD

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Impaza treatment of erectile dysfunction in patients with essential hypertension and CHD receiving cardiotropic therapy improved erectile function and increased reserve circulation. Addition of impaza to the treatment protocol in cardiological patients considerably increased perfusion and reduced the content of desquamated epitheliocytes. No side effects of impaza were noted.

Key Words: *erectile dysfunction; endothelial dysfunction; impaza; coronary heart disease*

Erectile dysfunction (ED) is observed in millions men all over the world and attracts much scientific and universal attention [10,11]. Cardiovascular diseases closely correlate with the development of ED [6,13], arterial hypertension is a common risk factor for ED. These pathologies are associated with increased peripheral vascular resistance and decreased endothelium-dependent vasodilation. Moreover, hypotensive drugs, in particular, α- and/or β-adrenoceptor blockers and guanidine derivatives can promote the development of ED.

Damage to endothelial cells is a cause of ED in 80% cases [2]. Endothelial dysfunction is a complex process. Impaired bioavailability of NO, reduced number of receptors (*e.g.* muscarinic) and increased activity of antiotensin-converting enzyme (ACE) on the surface of endothelial cells are the major manifestation of endothelial dysfunction. Neurogenous NO is the most important factor inducing dilatation of penile vessels, while NO produced by endothelial cells is essential for maintenance of erection [5]. In smooth muscle cells, NO activates the guanylate cyclase system, which leads to elevation of cGMP concentration in the cell [4]. cGMP activates specific protein kinase, which results in a decrease in intracellular Ca^{2+} concentration and relaxation of smooth muscle cells. In the cavernous tissue, cGMP is converted into 5'-GMP under the effect of specific type 5 phosphodiesterase. Thus, cGMP plays a key role in relaxation of cavernous body miscles and in the mechanism of erection on the whole, because it mediates both the neurogenous and endothelium-dependent mechanisms of relaxation of trabecular muscles [7].

The role of endothelial dysfunction in the development of CHD is well established [12]. This is a common feature of CHD and ED. Correction of endothelial insufficiency is a perspective trend in the therapy and a universal method of pathogenetic treatment of these diseases.

Here we evaluated the effect of impaza on NO synthase activity in patients with CHD and essential hypertension (EH) accompanied by ED.

MATERIALS AND METHODS

A total of 58 CHD patients, functional class II effort angina, and 68 patients with EH were examined. The mean age of patients was 55.6±1.4 years.

CHD patients were divided into two groups. Group 1 patients (n=21; mean age 56.4±1.3 years) received standard cardiotropic therapy: combined treatment with nitrates (monocinque, 20 mg once a day) and β-adrenoceptor blockers (concor, 2.5 mg once a day);

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ACE inhibitors (enalapril, 10 mg once a day), diuretics (hypothiazide, 12.5 mg once a day), and antioxidants (preductal, 20 mg twice a day) were administered, if needed. In group 2 (n=37; mean age 54.3±1.5 years), this standard cardiotropic therapy was supplemented with impaza (1 tablet once a day for 3 months).

The patients with EH (45-70 years, mean age 54.0±1.2 years) comprised group 3. Of them, EH history <5 years and 5-10 years was observed in 43 and 57%, respectively. Stages I, II, III, and IV of EH were revealed in 29, 35, 29, and 7% patients, respectively. Group 3 patients received standard hypotensive therapy including ACE inhibitors (enalapril, 10 mg once a day), β-adrenoceptor blockers (concor, 2.5 mg once a day), angiotensin receptor antagonists (teveten, 600 mg once a day), and calcium antagonists (amlodipine, 5 mg once a day). In group 4 (n=20), standard therapy for EH was supplemented with administration of impaza (1 bablet once a day for 3 months). All patients had ED.

Initial examination including interpretation of the clinical course of angina pectoris (score), evaluation of copulative function (MCF score) [3], laser Doppler flowmetry (LDF) from the projection of the heart with cuff test, and detection of desquamated endotheliocytes in the peripheral blood.

LDF was recorded on the inner surface of the forearm near the wrist joint (point of heart projection). Occlusion (cuff) test was performed by the standard method on a LAKK-02 laser microcirculation analyzer. For evaluation of microcirculation by LDF, the following parameters were calculated: myogenic tone, reserve blood flow, and endothelium-dependent component of the tone.

Miogenic tone (MT) of metarterioles and precapillary sphincters was determined as:

$$MT=\sigma\times P_{AV}/A_M\times M,$$

where σ is mean square deviation of the microcirculation parameter, P_{AV} is average blood pressure, A_M is the amplitude of myogenic range oscillations, and M is arithmetic mean of microcirculation parameter (in perfusion units). During the occlusion test, the initial and minimum M values ($M_{initial}$ and M_{min}) were recorded during 3-min occlusion and maximum M (M_{max}) was recorded during postocclusion hyperemia.

Reserve circulation (RC) is a range of possible changes of blood filling in the microcirculatory bed (reserve capacities of the microcirculatory bed):

$$RC=M_{max}/PM_{initial}\times 100\%,$$

where $PM_{initial}$ is parameter of microcirculation.

Initial perfusion was measured, then the cuff on the arm was inflated for 3 min and parameters of blood flow (M_{min}) were recorded, and then postocclusion hyperemia (M_{max}) was measured.

Endothelium-dependent component of the tone (EDCT) is presented by amplitudes of blood flow oscillations of endothelium-dependent origin (rel. units):

$$EDCT=\frac{\sigma\times P_{AV}}{A_E\times M},$$

where $A_E$is the amplitude of oscillations in endothelial range.

The only morphological criterion of the degree of endothelial damage is its desquamation, which can be evaluated by the number of circulating desquamated endotheliocytes in the peripheral blood. The number of desquamated endotheliocytes in blood plasma was determined by phase-contrast microscopy (normal 3.6± 0.4 cells per 100 μl).

RESULTS

In all patients, testing with MCF questionnaire revealed mild ED. In group 1, exercise tolerance increased and the intensity of pains decreased after 3-month treatment (Table 1).

LDF analysis revealed an increase in postocclusion hyperemia parameters and insignificant decrease in reserve blood flow parameter. After treatment, the myogenic tone slightly decreased, while endothelium-dependent component of the tone increased (Table 2).

The number of desquamated endotheliocytes in the peripheral blood decreased from 8.83±0.91 to 7.87± 0.85 cells per 100 μl, *i.e.* this parameter did not approximate the normal values.

In group 2, the mean MCF score significantly increased after therapy due to improvement of all three component of the copulation cycle. After therapy, parameters of postocclusion hyperthermia considerably increased, while parameter of reserve blood flow decreased, which is considered as recruitment of additional non-functioning capillaries into total microcirculation blood flow. The decrease in myogenic tone indirectly attests to relaxation of precapillary musculature, while the increased component of endothelium-dependent tonus indirectly indicated increased concentration of endothelium-dependent NO (Table 2).

The count of desquamated epitheliocytes in the peripheral blood of group 2 patients significantly decreased from 9.65±0.79 to 5.13±0.90 cells per 100 μl, *i.e.* this parameter was much close to the normal.

After therapy, the parameter of tissue perfusion considerably increased in group 2 patients, which attests to increased blood filling of the microcirculatory bed. Coefficient of reserve blood flow in group 1 and 2 before treatment was 231 and 232%, respectively; after therapy this parameter remained practically unchanged in group 1 and considerably decreased in group 2.

TABLE 1. Clinical Symptoms of CHD and ED in Patients of Groups 1 and 2 before and after Therapy (*M*±*m*)

Clinical symptom	Group 1		Group 2	
	before treatment	after treatment	before treatment	after treatment
Chest pain during rapid walking	5.8±0.2	3.50±0.34*	5.70±0.16	2.50±0.22*
Chest pain during quiet walking	4.70±0.35	4.56±0.23	4.68±0.41	2.13±0.09*
Chest pain at rest	3.00±0.18	3.10±0.18	3.30±0.24	1.03±0.16*
Constricting pain	5.70±0.23	3.10±0.31*	5.50±0.46	2.52±0.42*
Cramping pain	4.80±0.25	4.50±0.24*	4.90±0.23	2.06±0.30*
Retrosternal discomfort	2.00±0.04	1.56±0.36*	1.90±0.16	0.55±0.22*
Psychogenic component	3.18±0.70	3.26±0.45	3.22±0.65	4.10±0.45*
Copulative component	4.25±0.43	4.30±10.55	4.10±0.51	5.60±0.63*
Erectile component	3.36±0.20	3.34±0.31	3.50±0.65	5.20±0.72*

Note. Here and in Tables 2, 3: *$p<0.05$ compared to the corresponding values before treatment.

TABLE 2. LDF Parameters in Patients of Groups 1 and 2 before and after Therapy (*M*±*m*)

Parameter	Group 1		Group 2	
	before treatment	after treatment	before treatment	after treatment
$M_{initial}$	6.14±0.30	6.50±1.32	6.40±0.51	7.80±0.68*
σ	0.95±0.72	0.12±0.01	0.89±0.85	0.96±0.62
Variation coefficient	1.61±0.83	1.99±0.22	1.70±0.92	1.95±0.67*
M_{min}	5.85±0.32	5.90±1.06	5.56±0.43	6.82±0.49*
M_{max}	6.84±0.45	8.35±0.98*	6.70±0.37	7.46±0.45*
Reserve blood flow, %	231.00±0.09	229.00±7.56*	228.00±0.14	198.00±0.24*
Myogenic tone	0.486±0.230	0.467±0.670	0.489±0.120	0.398±0.430
Endothelium-dependent component of vascular tone	36.45±4.50	37.3±5.2	37.7±6.5	45.30±5.85*

Evaluation of treatment results in patients with EH showed that BP decreased by on average 20±3 mm Hg. Evaluation of ED with MCF scale showed that all three components remained unchanged in group 3. In patients receiving impaza (group 4), the psychogenic component increased from 3.06±0.58 to 4.30±0.35 ($p<0.05$), copulative component increased from 4.00±0.49 to 5.80±0.56 ($p<0.05$), and erectile component increased from 3.40±0.45 to 5.40±0.66 ($p<0.05$).

According LDF data, parameters of reserve blood flow decreased during impaza treatment (Table 3), which indicated an increase in the number of functioning capillaries. Myogenic tone also decreased, which indicated relaxation of precapillaries and contributed to BP decrease. Parameter of tissue perfusion also increased in group 4. It should be noted that signs of spastic circulatory disturbances were observed before therapy, but after treatment blood flow parameters approximated the physiological norm.

Thus, exercise tolerance increased in patients with CHD and effort angina against the background of therapy for cardiovascular disease and administration of impaza. In particular, we observed a decreased in the incidence of anginal attacks during mild and moderate exercise. Addition of impaza to the therapy of cardiological patients of this group increased the parameter of tissue perfusion, mean square deviation, which attests to improvement of coronary microcir-

TABLE 3. LDF Parameters in Patients of Groups 3 and 4 before and after Therapy ($M \pm m$)

Parameter	Group 3		Group 4	
	before treatment	after treatment	before treatment	after treatment
$M_{initial}$	6.0±0.4	6.40±1.02	6.02±0.36	8.00±0.75*
σ	0.88±0.60	0.71±0.02*	0.94±0.08	0.88±0.06
Variation coefficient	1.61±0.22	2.00±0.52	1.76±0.28	2.05±0.36*
M_{min}	6.05±0.36	6.12±0.48	5.88±0.53	6.98±0.51*
M_{max}	6.72±0.44	8.15±0.72*	6.74±0.32	7.58±0.36*
Reserve blood flow, %	215.00±8.09	228.00±7.56*	236.00±6.14	188.00±4.24*
Myogenic tone	0.472±0.180	0.458±0.280	0.492±0.280	0.388±0.230*
Endothelium-dependent component of vascular tone	39.36±3.50	38.4±6.2	38.7±2.4	46.4±1.8*

culatory blood flow. Impaza treatment increased the coefficient of reserve blood flow by 34%, which was virtually equivalent to enhancement of NO production. The decrease in the content of desquamated endotheliocytes can indicate improvement of the metabolism of vascular endothelium in the whole body. In patients with EH, addition of impaza to standard therapy not only improved microcirculation in the myocardium, but also reduced the severity of ED, which positively affects the course of the disease. The specified changes were absent in the control group. Impaza is a pathogenetic preparation for endothelial insufficiency on the whole, which extends the possibility of its application in complex therapy of patients with CHD, atherosclerosis, and EH. Impaza prevents the development of endothelial dysfunction, thus alleviating the course of the cardiovascular pathology and preventing ED.

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