УДК 616.13-004.6-092+615.22 DOI: http://doi.org/10.30978/TB2024-2-14

V.G. Lyzogub[1], V.I. Petrenko[1], O.M. Savchuk[2], O.G. Kupchynska[1, 3], T.M. Motsak[1], O.V. Dolynna[1], L.A. Kuzmenko[1], V.-S.M. Halich[1], D.S. Novyk[1]

[1] Bogomolets National Medical University, Kyiv, Ukraine
[2] NSC «Institute of Biology and Medicine» of Taras Shevchenko Kyiv National University, Kyiv, Ukraine
[3] SU «National Scientific Center named after Acad. M.D. Strazhesko National Academy of Sciences of Ukraine, Kyiv, Ukraine

Secondary Prevention of Multifocal Atherosclerosis Combined with Chronic Obstructive Pulmonary Disease

The problem of secondary prevention of multifocal atherosclerosis (MAS) combined with chronic obstructive pulmonary disease (COPD), is a leading cause of death in the world. Therefore, the search for drugs capable of affecting the destructive mechanisms underlying both MAS and COPD is an extremely urgent problem today.

Objective — to reduce the risks of destabilization of atherosclerotic plaques by reducing the levels of metallomatrix metalloproteases (MMP)-2 and MMP-9 in patients on MAS combined with COPD.

Materials and methods. The study included 62 men (68.1 ± 4.2) years old with MAS. All patients with MAS had clinical and functional signs of injury in coronary, cerebral and femoral vascular territories, 30 of these patients (group MAS-2) additionally had clinical and functional signs of COPD (GOLD-2). The control group (CG) consisted of 18 practically healthy men, aged (65.4 ± 3.7) years. Examination of the patients included echocardiography, dopplerography of the vessels of the neck and arteries of the lower extremities, determination of walking distance and ankle-brachial index, Holter ECG monitoring, spirography and determination of MMP-2 and MMP-9 levels in blood. Patients of both groups were prescribed cilostazol (50 mg twice a day) and GABA aminalon (250 mg twice a day) on the background of basic treatment. The course of treatment lasted 16 weeks.

Results and discussion. During the initial examination of patients, MAS-2 group showed significantly ($p < 0.001$) lower volumetric blood flow in the studied arteries, and significantly ($p < 0.01$) higher levels of MMP-2 and MMP-9, as compared to CG, as well as with patients of the MAS-1 group. After 16 weeks of treatment, with the addition of cilostazol and aminalon, the level of MMP in the blood significantly ($p < 0.05$) decreased in both groups, in particular, in the MAS-2 group, in patients with the combined pathology of MAS and COPD, a significant decrease was found MMP-2 by 23.6 % ($p < 0.01$), and MMP-9 by 12.1 % ($p < 0.05$). Volumetric blood flow indicators increased significantly ($p < 0.05$) in all studied vascular territories, which led to improvement in clinical manifestations of the disease — a decrease in the number of painful and painless episodes of myocardial ischemia, and an increase in walking distance.

Conclusions. The use of a complex therapy of statins, cilostazol and GABA in patients with MAS combined with COPD allows to reduce significantly the levels of MMP-2 and MMP-9, which ensures the stability of atheromatous plaques and significantly improves blood supply in vascular territories with atherosclerotic lesions.

Keywords

Chronic obstructive pulmonary disease, multifocal atherosclerosis, metalloproteases, volumetric blood flow.

Chronic obstructive pulmonary disease (COPD) and multifocal atherosclerosis (MAS) are chronic diseases that have in common the fact that they each have a negative effect on the supply of oxygen to all organs and tissues of the human body. This circumstance determines the extreme urgency of researching the peculiarities of the clinical manifestations of their combination, taking into account

the high dependence of the vital activity of the brain and heart muscle on the supply of oxygen.

COPD is a heterogeneous disease, which today is the third cause of death worldwide [2, 23], giving way to cardiovascular pathology of atherosclerotic origin. COPD is responsible for approximately three million deaths and high global health costs [2, 23]. It has been established that concomitant cardiovascular diseases (CVD) significantly increase mortality associated with COPD, with about 30 % of all COPD patients dying as a result of cardiovascular manifestations [1, 13]. Currently, atherosclerosis is the leading cause of cerebral circulation disorders, peripheral artery disease, and coronary heart disease (CHD) [6, 10]. The most severe manifestation of atherosclerosis is multifocal, or generalized atherosclerosis, with simultaneous damage to two or more vascular territories, more often — coronary, cerebral, femoral. Numerous clinical studies indicate a deterioration of the course and an increase in mortality in the combination of COPD and atherosclerosis [4, 14, 20].

One of the main reasons for the development of cardiovascular complications and mortality is the formation and destabilization of atherosclerotic plaques (AP). As evidenced by numerous experimental and clinical data, zinc-containing matrix metalloproteases (MMPs) play a leading role in AP destabilization [9, 16, 21]. It is known that patients with a high frequency of repeated cardiovascular events are characterized by an increase in the level of MMP-2 and MMP-9 in AP [17, 18, 21]. A direct correlation between elevated levels of MMP-2 and MMP-9 in the blood and the mortality of patients with myocardial infarction was revealed [9, 12].

Numerous cross-sectional studies have reported elevated MMP-9 levels in cohorts of patients with COPD and the presence of an inverse relationship between forced expiratory volume in 1 second (FEV1) and serum MMP-2 levels [15]. In two established cohorts of COPD patients, «PIROMICS» and «COPD Gene», elevated plasma MMP-9 concentrations were associated with COPD exacerbations. High levels of MMP-9 were observed in both cohorts with pronounced destructive changes in the bronchopulmonary structure of the lungs [22]. Today, it is known that the leading role in the destruction of the extracellular matrix belongs to MMPs, whose activity leads to the remodeling of the respiratory tract through cycles of damage and restoration of the extracellular matrix, the formation of pneumosclerosis and emphysema of the lungs [7, 22]. In addition, circulating levels of MMP-2 and MMP-9 can be indicators of the effectiveness of therapy in patients with CVD [12].

Considering the fact that COPD and MAS independently of each other lead to an increase in MMP levels, compared to their reference values, patients with comorbid pathology (COPD + MAS) are at risk of developing cardiovascular complications associated with a significant increase in serum levels of MMP-9 and destabilization of AP. Researchers consider MMP-9 to be an independent predictor of AP destabilization [22].

Clinical and experimental studies have shown that antibiotics of the tetracycline group and statins are really effective means of reducing the levels of MMP-2 and MMP-9 and improving the course of CVD and COPD. Thus, doxocycline was effective in patients with acute myocardial infarction. In the «TIP-TOP study», doxocycline reduced myocardial infarct size and improved myocardial contractility in patients with ST-elevation acute myocardial infarction and left ventricular dysfunction [3].

It is known that the long-term use of statins in both COPD and atherosclerosis reduces mortality. The results of a multi-ethnic, population-based prospective study in which 5,280 patients participated showed that statin treatment reduces the likelihood of developing both CHD and CVD in general (by 14 and 23 %, respectively), and overall mortality (by 18 %) [19]. Lu and others, found that the use of statins in patients with COPD significantly reduced all-cause and CVD-related mortality, as well as COPD exacerbations, while reducing C-reactive protein (CRP) levels and the severity of pulmonary hypertension [11].

These data were confirmed by the results of the Copenhagen population-based study, which revealed a decrease in CRP levels in the blood and the likelihood of disease exacerbations in patients with COPD and concomitant CVD while taking statins [5]. According to the data of the multicenter clinical study «EASY-FIT», long-term use of atorvastatin contributed to an increase in the thickness of the fibrous cap and stability of AP, as well as a decrease in the level of MMP-9 in patients with coronary artery disease [8].

Giving credit to statins, their effect on MMP is insufficiently effective, especially in patients with multifocal atherosclerosis with damage to several vascular territories.

Secondary prevention and simultaneous treatment of COPD and MAC is a rather difficult problem of practical medicine, given the fact that the main drugs used in the treatment of these diseases have the opposite direction. Effects on beta-adrenergic receptors, long-term use of corticosteroids in patients with MAC is undesirable, use of cholinolytics, theophylline or double LAMA/LABA, or triple therapy increase cardiovascular risk in patients with COPD. Accumulated data from randomized controlled trials based on the analysis of the end points

of acute myocardial infarction and stroke showed that combined COPD therapy is dangerous in patients with atherosclerosis [24].

In recent years, there has been an active search for drugs capable of controlling MMP levels. In our opinion, medicinal products that can be used in patients with MAS and COPD should meet three main requirements: first, they should not worsen the course of these diseases (neither COPD nor atherosclerosis), second, they should have a gerontological orientation, taking into account the age of the patients, and third, monitoring MMP-2 and MMP-9 levels.

Objective — to reduce the risks of destabilization of atherosclerotic plaques by reducing the levels of MMP-2 and MMP-9 in patients on multifocal atherosclerosis combined with chronic obstructive pulmonary disease.

Materials and methods

The study included 62 male patients, average age (68.1 ± 4.2) years with clinical manifestations of MAS, among whom 30 had COPD manifestations. The control group (CG) consisted of 18 practically healthy men, comparable in age (65.4 ± 3.7) years. All patients with MAS had clinical manifestations of intermittent claudication syndrome of atherosclerotic genesis (stage I—II according to the Fontaine—Pokrovsky classification). Patients with MAS were divided into two groups. The group MAS-1 consisted of 32 patients, 11 of whom had a history of ischemic stroke, 21 had an acute myocardial infarction (MI). The group MAS-2 consisted of 30 patients with clinical signs of atherosclerotic encephalopathy, of which 13 had a history of stroke, and 19 — MI. All patients of the group MAS-2 had clinical and functional signs of COPD (GOLD-2, moderate severity (FEV1 from 50 to 79 % of normal)). 11 and 9 patients had concomitant arterial hypertension (AH), compensated diabetes mellitus (DM) in 10 and 7, cigarette smoking — 9 and 28 (on average 1 pack/day), patients of groups MAS-1 and MAS-2, respectively. All patients before inclusion in the study received information about the nature of the study and signed an informed consent to participate in the study.

Exclusion criteria were as follows: history of hemorrhagic stroke, stroke up to 12 months before inclusion in the study, life-threatening heart rhythm disorders (ventricular, prolongation of the Q-T interval), stage IIA heart failure and above (according to the classification of M. Strazhesko—V. Vasilenko), history of gastrointestinal or other bleeding, liver or kidney failure (creatinine clearance < 25 ml/min), uncontrolled hypertension, oncological diseases.

A general clinical examination was performed on all patients; the level of MMP-2 and MMP-9 in blood plasma was determined by enzyme immunoassay (ELISA). The ankle-brachial index (ABI) was also determined. Using ultrasound-doppler (Hitachi, Aloka, ArriettaS70 device), volume flow (FV) and peak systolic velocity (PSV) parameters were determined in the carotid — *a. carotis interna* (ACI), arteries of the lower extremities — *a. femoralis communis* (AFC) and *a. tibialis posterior* (ATP), determined the degree of arterial stenosis. The number and duration of episodes of myocardial ischemia (MI) were determined with the help of Holter ECG monitoring (HM ECG), (KHAI-MEDICA Cardio Sens K device). Painless walking distance (PWD) and maximum walking distance (MWD) and cognitive function were determined.

In patients with COPD, research was carried out by the method of spirography (spirograph) before and after the use of bronchodilators to determine the type of violation of lung ventilation and bronchial patency; the degree and reversibility of bronchial obstruction — narrowing of the bronchs, which forms such phenomena as shortness of breath and suffocation attack (RR — respiratory rate (min^{-1}); TV — tidal volume (L); VC — vital capacity of the lungs (%); RVi — inspiratory reserve volume (L); RVe — expiratory reserve volume (L); RV — residual volume; TLC — total lung capacity; FVC — forced vital capacity of the lungs (L); FEV_1 — forced expiratory volume in the first second (L); FEV_1/FVC, % — Typhno index (%); FEV_{25-75} — Maximum expiratory volume rate (L/s)).

Patients of both groups of MAS received basic therapy, which included: acetylsalicylic acid (ASA), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARB-II), calcium antagonists, β-blockers and low doses of diuretics (if necessary) and, necessarily, statins. In addition, patients received cilostazol (50 mg twice a day) and GABA aminalon (250 mg twice a day). Patients in groups MAS-1 and MAS-2 were examined twice — before the appointment of additional treatment and 16 weeks after. CG was examined only during the initial examination. This study complied with the ethical principles of the Helsinki Declaration of the World Medical Association of Physicians (revision 2008), ethical and moral requirements according to the Order of the Ministry of Health of Ukraine No. 281 dated November 1, 2000, including anonymity, confidentiality and charity.

Statistical analysis of the data was performed using the IBM SPSS program, version 23, R. The normality of the distribution of the obtained data was performed by the Shapiro—Wilk method. With a normal distribution of data, the arithmetic mean value of the indicator (M) and standard deviation (± SD) were determined, when comparing the

Table 1. **Doppler ultrasound indicators in patients of both groups before and after treatment**

Arteries	Measurements	Control group (n = 18)	MAS-1 (n = 32)		MAS-2 (n = 30)	
			Before treatment	After treatment	Before treatment	After treatment
ACI	PSV, cm/s	74.8 (62.7; 85.6)	137.2 (98.3; 132.6)##	118.4 (75.1; 121.3)**	146.7 (125.6; 155.2)##	131.5 (116.8; 143.6)*
	FV, mL/min	246.5 (186.5; 256.2)	183.5 (172.7; 231.4)##	218.7 (181.4; 254.5)*	154.2 (149.5; 177.8)###	179.9 (161.2; 210.4)*
AFC	PSV, cm/s	72.4 (58.2; 81.4)	76.2 (62.8; 83.3)#	72.8 (54.2; 96.7)	79.6 (69.2; 87.7)#	73.4 (66.8; 83.2)
	FV, mL/min	203.7 (167.4; 224.1)	89.6 (72.7; 97.4)###	110.7 (87.4; 132.6)**	78.3 (64.7; 83.8)###	95.7 78.4; 115.3)**
ATP	PSV, cm/s	47.8 (36.9; 62.4)	81.4 (68.1; 96.5)##	69.3 (53.8; 95.9)**	82.5 (73.4; 97.6)##	73.8 (59.4; 82.1)**
	FV, mL/min	12.4 (8.7; 13.7)	3.9 (3.1; 5.8)###	5.4 (5.1; 7.7)***	3.4 (3.1; 5.0)###	4.7 (3.5; 6.8)***

Note. the difference in the values of the indicator compared to CG is significant: # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$; the dynamics of the indicator during treatment is reliable: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2. **Levels of MMP-2 and MMP-9 in patients of both groups before and after treatment**

Groups of patients		MMP-2, CU/mg protein	MMP-9, CU/mg protein
Control group (n = 18)		0.109 (0.08; 0.113)	0.110 (0.09; 0.112)
MAS-1 (n = 32)	Before treatment	0.169 (0.154; 0.192)##	0.178 (0.159; 0.187)##
	After treatment	0.124 (0.118; 0.156)#**	0.155 (0.137; 0.172)#*
MAS-2 (n = 30)	Before treatment	0.182 (0.163; 0.198)##	0.207 (0.178; 0.224)##
	After treatment	0.139 (0.113; 0.149)#**	0.182 (0.169; 0.197)##*

Note. The difference in the values of the indicator compared to CG is significant: # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$; the dynamics of the indicator during treatment is reliable: * $p < 0.05$; ** $p < 0.01$; *** < 0.001.

values, the Student's t-test was used. When the data distribution was different from the normal distribution, the Wilcoxon test was used, the median, first and third quartiles (Me (Q1; Q3)) were calculated, when comparing the values, the method of paired samples was used, χ^2 was also used; univariate analysis of variance. The difference between the data samples was considered reliable at $p < 0.05$.

Results and discussion

All patients included in the study had intermittent claudication. Clinically, it was manifested by heaviness in the lower limbs, the need to stop while walking; instrumentally, this was confirmed by the determination of the ABI, which in the group MAS-1 was (0.68 ± 0.07), and in the group MAS-2 — (0.65 ± 0.08), while in the control group — (0.91 ± 0.07). The lack of difference between the ABI values in the MAS-1 and MAS-2 groups indicates a comparable lesion of the arteries of the lower extremities in patients of these groups.

During the Doppler examination in patients of both groups of MAS, APs were detected in all studied vessels (ACI, AFC, ATP) with a narrowing of their lumen from 25 to 74 %. APs with signs of their instability [14] were detected in the carotid and lower limb arteries in patients of both groups: in ACI — in 68.5 and 76.4 %, in AFC — in 73.4 and 78.9 % of patients, respectively, of MAS-1 and MAS-2 groups.

In patients of both groups, the indicators of volumetric blood flow in the examined arteries were significantly ($p < 0.05$) lower, compared to the control group (Table 1). All patients had intermittent claudacion, first of all, FV indicators in the arteries of the lower extremities pay attention to themselves. So, before the treatment, the FV in the MAS-1 and MAS-2 groups were lower than in the control group, in all studied vessels: in AFC by 2.3 and 2.6 times ($p < 0.001$), in ATP — by 3.2 and 3.6 times ($p < 0.001$), in ACI — by 1.3 and 1.6 times ($p < 0.001$), respectively. More significant changes in volume blood flow in the MAS-2 group may be due to the presence of COPD.

Determination of the initial level of MMP in both groups of MAS also differed significantly ($p < 0.05$) compared to CG (Table 2). It is noteworthy that in the MAS-1 group the levels of MMP-2 and MMP-9 were significantly ($p < 0.01$) higher by 1.5 and 1.6 times ($p < 0.01$) compared to the control group. While in the MAS-2 group: the level of MMP-2 was 1.7 times ($p < 0.01$), and MMP-9 was 1.9 times ($p < 0.01$) higher, compared from CG. The data obtained by us coincide with the data of the literature [12, 15, 22], which once again confirms the dependence of the MMP level, especially MMP-9,

Table 3. **Spirography indicators in patients of the MAS-2 group (n = 30) before and after treatment**

Measurements	Proper	Before treatment		After treatment	
		Abs.	%	Abs.	%
RR, min^{-1}		14.00 ± 3.12		16.00 ± 2.16	
TV, L		0.92 ± 0.08		0.94 ± 0.05	
MV, L		12.86 ± 3.17		14.96 ± 2.14	
VC, L	3.80 ± 0.11	3.5 ± 0.13	82.10 ± 1.26	3.6 ± 0.27	87.43 ± 4.72
RVi, L		1.43 ± 0.07		1.28 ± 0.08	
RVe, L		1.22 ± 0.03		1.19 ± 0.06	
RV	0.76 ± 0.04	0.90 ± 0.08	152.50 ± 12.71	0.82 ± 0.06	161.2 ± 13.52
TLC	4.56 ± 1.27	4.85 ± 0.56	106.40 ± 9.73	4.74 ± 0.26	103.23 ± 9.85
FVC, L	3.90 ± 0.28	4.06 ± 1.02	104.10 ± 10.20	4.04 ± 0.52	102.15 ± 9.75
FEV_1, L	3.24 ± 0.08	2.24 ± 0.31	69.10 ± 5.31	2.65 ± 0.32	75.12 ± 4.54
FEV_1/FVC, %		55.20 ± 4.72		62.61 ± 5.43	
FEV_{25}, L/s	6.39 ± 1.32	2.54 ± 0.18	71.0 ± 6.27	3.73 ± 0.42	82.6 ± 5.32
FEV_{50}, L/s	4.81 ± 0.31	2.47 ± 0.22	51.3 ± 4.17	3.58 ± 0.72	56.7 ± 2.72
FEV_{75}, L/s	2.53 ± 0.17	2.2 ± 0.12	34.4 ± 2.35	3.11 ± 0.26	51.6 ± 3.72

Note. Test with salbutamol: increase FEV_1 (6.0 ± 3.2) %.

on the presence of COPD and destructive changes in the bronchopulmonary structure of the lungs.

Also, significantly higher levels of MMP-2 and MMP-9 in MAS groups, compared to CG, are associated with a high risk of recurrent MI or death from MI and instability of atherosclerotic plaque and degree of arterial stenosis in patients with CHD [9, 16].

Another aggravating factor in patients of the MAS group, in particular in the MAS-2 group, is the presence of COPD. As can be seen from Table 3, the spirometry data improved, however, did not significantly change in the patients of the MAS-2 group after the treatment and corresponded to the GOLD-2.

After the treatment with the addition of cilostazol and GABA based on taking statins in patients of both groups of MAS, an improvement in the clinical picture was observed (reduction of pain sensations, paresthesias, numbness in the lower limbs when walking), which was confirmed by doppler. As a result of the treatment for 16 weeks, the volume blood flow indicators increased compared to the initial indicators (Figure). Thus, in the arteries of the lower extremities of patients of the MAS-1 and

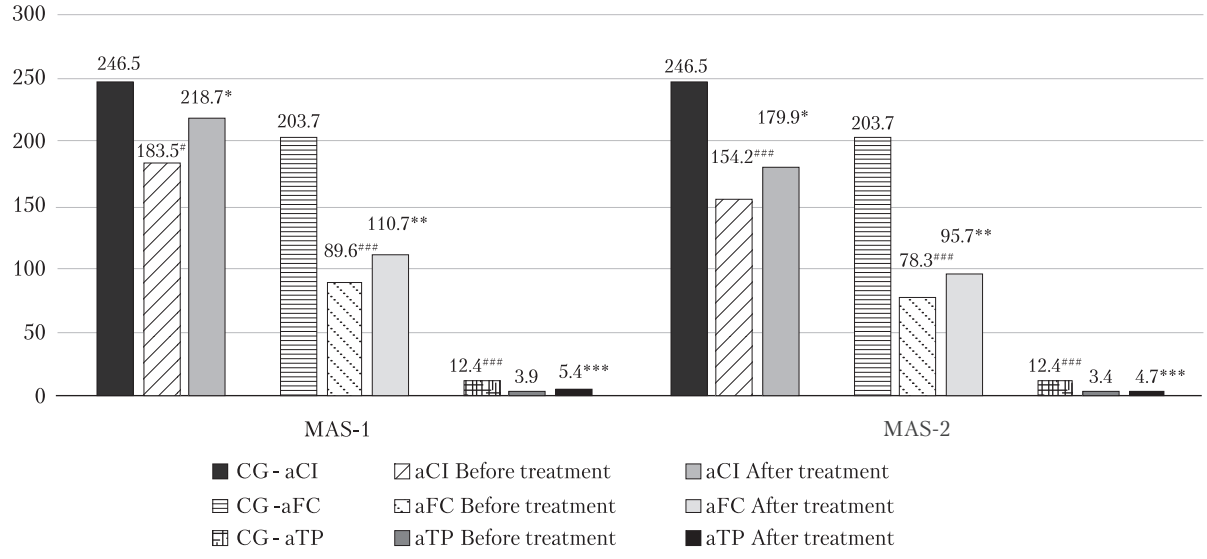

Figure. **Indicators of volumetric blood flow in patients of both groups of MAS before and after treatment**

The difference in the values of the indicator compared to CG: # p < 0.05; ## p < 0.01; ### p < 0.001; the dynamics of the indicator during treatment is reliable: * p < 0.05; ** p < 0.01; *** p < 0.001.

MAS-2 groups, the volumetric blood flow significantly increased, respectively: in ATP — by 38.4 and 38.2 %, in AFC — by 23.5 and 22.2 % ($p < 0.001$ in all cases). The dynamics of Doppler indicators corresponded to an increase ($p < 0.01$) in the walking distance in patients of both groups: PWD — by 54.2 % in the MAS-1 group and by 49.4 % in the MAS-2 group, and MWD, by 41.7 and 42.1 %, respectively.

Volumetric blood flow in the carotid arteries also increased ($p < 0.05$) in patients of both groups: in the MAS-1 group by 19.2 %, and in the MAS-2 group by 16.7 %. Against this background, an improvement in cognitive function was observed, in particular memory and attention. The frequency of episodes of myocardial ischemia (EMI) decreased ($p < 0.05$), both painful (PEMI) and painless (PlEMI) in both groups: in the MAS-1 by 15.4 and 14.6 %, and in the MAS-2 group by 13.2 and 12.8 %, respectively.

After the treatment, a positive dynamics of MMP was observed (see Table 2) in both groups of MAS: a significant decrease of MMP-2 ($p < 0.01$) — by 26.6 and 23.6 % and MMP-9 ($p < 0.05$) — by 12.9 and 12.1 %, respectively, in groups MAS-1 and MAS-2. Taking into account the known data from the literature regarding the existence of a positive relationship between the decrease in the activity of MMP-2 and MMP-9 and the stabilization of blood pressure and the reduction of the risk of repeated cardiovascular events, the dynamics of MMP under the influence of the combined treatment that we found indicate its positive effect not only on clinical manifestations and hemodynamic indicators, but also on AP stabilization [9, 16, 21].

Thus, the problem of treatment and secondary prevention of the combination of two diseases that are among the top three causes of mortality in the world — MAS and COPD, is caused by the confrontation of the mechanism of action of the main drugs used to treat these diseases. Moreover, this largely explains the high morbidity and mortality of patients who have a combination of MAS and COPD, which is significantly higher than mortality in patients with one pathology, monopathology — MAS or COPD.

The work presented by us is aimed at finding drugs capable of affecting the destructive mechanisms underlying both MAS and COPD. Numerous studies [7, 15, 17, 18, 21, 22] testify to the leading role of MMP in the development of destructive changes of both the bronchopulmonary system in patients with COPD and vascular atherosclerotic lesions of the arterial territories in patients with MAS. For this purpose, we used a combination of statins with cilostazol and aminalon.

Our studies have shown that a 16-week course of the combination of the above-mentioned drugs against the background of basic treatment leads to a significant decrease in plasma levels of MMP-2 and MMP-9, both in patients with isolated MAS and in patients with combined pathology of MAS and COPD. The specified dynamics of MMP was observed against the background of a significant decrease in the frequency of occurrence of PEMI and PlEMI, improvement of hemodynamic indicators, in particular, increase of volume blood flow indicators in the studied arteries, clinical reduction of COPD manifestations, reduction of intermittent claudication and improvement of cognitive functions.

Conclusions

1. In patients with the combined pathology of MAS and COPD, the level of MMP-2 and MMP-9 in blood plasma exceeded their levels in the group of MAS patients by 7.7 and 16.3 % (in both cases; $p < 0.05$) and 1.7 and 1.9 times (in both cases; $p < 0.01$), respectively, compared to the reference values of these indicators, despite long-term basic therapy.

2. In patients with the combined pathology of MAS and COPD adding to the standard therapy cilostazol and aminalon contributes to a significant reduction of MMP-2 and MMP-9 by 23.6 % ($p < 0.01$) and 12.1 % ($p < 0.05$), respectively.

3. Under the influence of complex treatment with the addition of cilostazol and GABA in patients with MAS combined with COPD, a significant increase in volume blood flow in femoral arteries was observed (in AFC by 22.2 %; $p < 0.01$; in ATP by 38.2 %; $p < 0.001$) and cerebral (in ACI by 16.7 %; $p < 0.05$) territories, as well as a decrease ($p < 0.01$) in the manifestations of intermittent lameness and the number of painful and painless episodes of myocardial ischemia.

The author declares that he has **no conflict of interest.**

Funding sources. The execution of this study and the writing of the manuscript were accomplished without external funding.

References

1. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. Eur Heart J Acute Cardiovasc Care. 2012 Apr;1(1):60-74. doi: 10.1177/2048872612441582. PMCID: PMC3760546.
2. Brassington K, Selemidis S, Bozinovski S, Vlahos R. Chronic obstructive pulmonary disease and atherosclerosis: common mechanisms and novel therapeutics. Clin Sci (Lond). 2022 Mar 31;136(6):405-23. doi: 10.1042/CS20210835. PMID: 35319068; PMCID: PMC8968302.
3. Cerisano G, Buonamici P, Valenti R, et al. Early short-term doxycycline therapy in patients with acute myocardial infarction and left ventricular dysfunction to prevent the ominous progression to adverse remodelling: the TIPTOP trial. Eur Heart J. 2014 Jan;35(3):184-91. doi: 10.1093/eurheartj/eht420. Epub 2013 Oct 8. PMID: 24104875.
4. Chandra D, Gupta A, Strollo PJ Jr, et al. Airflow limitation and endothelial dysfunction. Unrelated and Independent Predictors of Atherosclerosis. Am J Respir Crit Care Med. 2016;194(1):38-47. doi: 10.1164/rccm.201510-2093OC. PMID: 26771278; PMCID: PMC4960631.
5. Damkjær M, Håkansson K, Kallemose T, Ulrik CS, Godtfredsen N. Statins in High-Risk Chronic Obstructive Pulmonary Disease Outpatients: No Impact on Time to First Exacerbation and All-Cause Mortality — The STATUETTE Cohort Study. Int J Chron Obstruct Pulmon Dis. 2021 Mar 5;16:579-589. doi: 10.2147/COPD.S296472. Erratum in: Int J Chron Obstruct Pulmon Dis. 2021 Aug 19;16:2393-2395. PMID: 33707941; PMCID: PMC7943323.
6. Fan J, Watanabe T. Atherosclerosis: Known and unknown. Pathol Int. 2022 Mar;72(3):151-60. doi: 10.1111/pin.13202. Epub 2022 Jan 25. PMID: 35076127.
7. Houghton AM. Matrix metalloproteinases in destructive lung disease. Matrix Biol. 2015 May-Jul;44-46:167-74. doi: 10.1016/j.matbio.2015.02.002. Epub 2015 Feb 14. PMID: 25686691.
8. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. J Am Coll Cardiol. 2014 Dec 2;64(21):2207-17. doi: 10.1016/j.jacc.2014.08.045. Epub 2014 Nov 24. PMID: 25456755.
9. Lahdentausta L, Leskelä J, Winkelmann A et al. Serum MMP-9 diagnostics, prognostics, and activation in acute coronary syndrome and its recurrence. J Cardiovasc Transl Res. 2018 Jun;11(3):210-20. doi: 10.1007/s12265-018-9789-x. Epub 2018 Jan 18. PMID: 29349668; PMCID: PMC5974001.
10. Libby P. The changing landscape of atherosclerosis. Nature. 2021 Apr;592(7855):524-33. doi: 10.1038/s41586-021-03392-8. Epub 2021 Apr 21. PMID: 33883728.
11. Lu Y, Chang R, Yao J, Xu X, Teng Y, Cheng N. Effectiveness of long-term using statins in COPD — a network meta-analysis. Respir Res. 2019 Jan 23;20(1):17. doi: 10.1186/s12931-019-0984-3. PMID: 30674312; PMCID: PMC6343315.
12. Mashaqi S, Mansour HM, Alameddin H, et al. Matrix metalloproteinase-9 as a messenger in the cross talk between obstructive sleep apnea and comorbid systemic hypertension, cardiac remodeling, and ischemic stroke: a literature review. J Clin Sleep Med. 2021 Mar 1;17(3):567-91. doi: 10.5664/jcsm.8928. PMID: 33108267; PMCID: PMC7927322.
13. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? Ther Adv Respir Dis. 2018 Jan-Dec;12:1753465817750524. doi: 10.1177/1753465817750524. PMID: 29355081; PMCID: PMC5937157.
14. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? Ther Adv Respir Dis. 2018 Jan-Dec;12:1753465817750524. doi: 10.1177/1753465817750524. PMID: 9355081.
15. Navratilova Z, Kolek V, Petrek M. Matrix Metalloproteinases and Their Inhibitors in Chronic Obstructive Pulmonary Disease. Arch Immunol Ther Exp (Warsz). 2016 Jun;64(3):177-93. doi: 10.1007/s00005-015-0375-5. Epub 2015 Nov 26. PMID: 26611761.
16. Olejarz W, Łacheta D, Kubiak-Tomaszewska G. Matrix metalloproteinases as biomarkers of atherosclerotic plaque instability. Int J Mol Sci. 2020 May 31;21(11):3946. doi: 10.3390/ijms21113946. PMID: 32486345; PMCID: PMC7313469.
17. Picano E, Paterni M. Ultrasound tissue characterization of vulnerable atherosclerotic plaque. Int J Mol Sci. 2015 May 5;16(5):10121-33. doi: 10.3390/ijms160510121. PMID: 25950760; PMCID: PMC4463636.
18. Spacek M, Zemanek D, Hutyra M, Sluka M, Taborsky M. Vulnerable atherosclerotic plaque - a review of current concepts and advanced imaging. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2018 Mar;162(1):10-7. doi: 10.5507/bp.2018.004. Epub 2018 Feb 21. PMID: 29467545.
19. Talbot D, Delaney JAC, Sandfort V, Herrington DM, McClelland RL. Importance of the lipid-related pathways in the association between statins, mortality, and cardiovascular disease risk: The Multi-Ethnic Study of Atherosclerosis. Pharmacoepidemiol Drug Saf. 2018 Apr;27(4):365-72. doi: 10.1002/pds.4393. Epub 2018 Feb 6. PMID: 29405501; PMCID: PMC5937846.
20. Topsakal R, Kalay N, Ozdogru I, et al. Effects of chronic obstructive pulmonary disease on coronary atherosclerosis. Heart Vessels. 2009 May;24(3):164-8. doi: 10.1007/s00380-008-1103-4. Epub 2009 May 24. PMID: 19466515.
21. Wang X, Khalil RA. Matrix metalloproteinases, vascular remodeling, and vascular disease. Adv Pharmacol. 2018;81:241-330. doi: 10.1016/bs.apha.2017.08.002. Epub 2017 Sep 19. PMID: 29310800; PMCID: PMC5765875.
22. Wells JM, Parker MM, Oster RA, et al. Elevated circulating MMP-9 is linked to increased COPD exacerbation risk in SPIROMICS and COPDGene. JCI Insight. 2018 Nov 15;3(22):e123614. doi: 10.1172/jci.insight.123614. PMID: 30429371; PMCID: PMC6302944.
23. World Health Organization (2020) The top 10 causes of death: World Health Organization. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death [Google Scholar].
24. Yang M, Li Y, Jiang Y, Guo S, He JQ, Sin DD. Combination therapy with long-acting bronchodilators and the risk of major adverse cardiovascular events in patients with COPD: a systematic review and meta-analysis. Eur Respir J. 2023 Feb 9;61(2):2200302. doi: 10.1183/13993003.00302-2022. PMID: 36137586.

В.Г. Лизогуб[1], В.І. Петренко[1], О.М. Савчук[2], О.Г. Купчинська[1, 3], Т.М. Моцак[1], О.В. Долинна[1], Л.А. Кузьменко[1], В.-С.М. Галіч[1], Д.С. Новік[1]

[1] Національний медичний університет імені О.О. Богомольця, Київ
[2] ННЦ «Інститут біології та медицини» Київського національного університету імені Тараса Шевченка, Київ
[3] ДУ «Національний науковий центр імені акад. М.Д. Стражеска НАМН України», Київ

Вторинна профілактика мультифокального атеросклерозу, поєднаного із хронічним обструктивним захворюванням легень

Проблема вторинної профілактики мультифокального атеросклерозу (МАС), поєднаного з хронічним обструктивним захворювання легень (ХОЗЛ), є однією з основних причин смертності в світі. Тому пошук лікарських засобів, здатних впливати на деструктивні механізми, що лежать в основі як МАС, так і ХОЗЛ, є актуальною проблемою.

Мета роботи — знизити ризик дестабілізації атеросклеротичних бляшок за рахунок зменшення рівня матриксних металопротеаз (ММП) 2 і 9 у пацієнтів із МАС у поєднанні з ХОЗЛ.

Матеріали та методи. У дослідження було залучено 62 чоловіків із МАС. Середній вік — (68,1 ± 4,2) року. Усі пацієнти мали клінічні та функціональні ознаки враження коронарного, церебрального та феморального судинних басейнів, 30 із них (група МАС-2) — клінічні та функціональні ознаки ХОЗЛ (GOLD-2), 32 (група МАС-1) — не мали ознак ХОЗЛ. Контрольну групу (КГ) утворили 18 практично здорових чоловіків. Середній вік — (65,4 ± 3,7) року. Обстеження пацієнтів передбачало проведення ехокардіографії, доплерографії судин шиї та артерій нижніх кінцівок, визначення дистанції ходьби та кісточково-плечового індексу, холтерівське моніторування електрокардіограми, спірографію та визначення рівня ММП-2 та ММП-9 у плазмі крові. Пацієнтам обох груп на тлі базового лікування призначали цилостазол (50 мг двічі на добу) та препарат γ-аміномасляної кислоти аміналон (250 мг двічі на добу). Курс лікування тривав 16 тиж.

Результати та обговорення. При первинному обстеженні пацієнтів хворі групи МАС-2 мали статистично значущо ($p < 0,001$) нижчі показники об'ємного кровотоку в досліджуваних артеріях і статистично значущо ($p < 0,01$) вищі рівні ММП-2 та ММП-9 порівняно з КГ та хворими групи МАС-1. Після 16-тижневого лікування з додаванням цилостазолу й аміналону вміст у крові ММП статистично значущо ($p < 0,05$) знизився в обох групах, зокрема в групі МАС-2 рівень ММП-2 — на 23,6 % ($p < 0,01$), рівень ММП-9 — на 12,1 % ($p < 0,05$). Показники об'ємного кровотоку статистично значущо ($p < 0,05$) збільшилися в усіх досліджуваних судинних басейнах, що сприяло поліпшенню клінічних виявів захворювання — зменшенню кількості больових та безбольових епізодів ішемії міокарда, збільшення дистанції ходьби.

Висновки. Застосування комплексної терапії (статинів, цилостазолу та γ-аміномасляної кислоти) у хворих на МАС у поєднанні з ХОЗЛ дає змогу статистично значущо знизити рівень ММП-2 і ММП-9, що забезпечує стабільність атероматозних бляшок та значно поліпшує кровопостачання в судинних басейнах з атеросклеротичним ураженням.

Ключові слова: хронічне обструктивне захворювання легень, мультифокальний атеросклероз, металопротеази, об'ємний кровотік.

Контактна інформація / *Corresponding author*

Моцак Тетяна Михайлівна, PhD, доцент кафедри внутрішньої медицини № 4
https://orcid.org/0000-0002-5545-8583
E-mail: tetianamihalovna@gmail.com

Стаття надійшла до редакції/Received 15.02.2024.
Стаття рекомендована до опублікування/Accepted 22.03.2024.

ДЛЯ ЦИТУВАННЯ

- Lyzogub VG, Petrenko VI, Savchuk OM, Kupchynska OG, Motsak TM, Dolynna OV, Kuzmenko LA, Halich V-SM, Novyk DS. Secondary Prevention of Multifocal Atherosclerosis Combined with Chronic Obstructive Pulmonary Disease. Туберкульоз, легеневі хвороби, ВІЛ-інфекція. 2024;2:14-21. doi: 10.30978/TB2024-2-14.
- Lyzogub VG, Petrenko VI, Savchuk OM, Kupchynska OG, Motsak TM, Dolynna OV, Kuzmenko LA, Halich V-SM, Novyk DS. Secondary Prevention of Multifocal Atherosclerosis Combined with Chronic Obstructive Pulmonary Disease. Tuberculosis, Lung Diseases, HIV Infection (Ukraine). 2024;2:14-21. http://doi.org/10.30978/TB2024-2-14.