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NDOTHELIAL DYSFUNCTION INFLUENCE ON THE MAIN PATHOGENETIC MECHANISMS OF ISCHEMIC HEART DISEASE PROGRESSION COMBINED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Keyword: *coronary heart disease, endothelin-1.*

Abstract. *The study involved 113 patients with stable exertional angina II-III functional class. Determination of endothelin-1 levels in blood plasma, activity of free radical processes and antioxidant protection, proteolysis and fibrinolysis was conducted. It has been proved that the course of coronary heart diseasewith concomitant chronic obstructive pulmonary disease is characterized by increasing intensity of free-radical lipids oxidation at the expense of increasing malonic aldehyde 10,1% ($p<0,05$) levels at reduced functioning of antioxidant catalase activity with a reduction to 11,4% ($p<0,05$) and increased levels of ceruloplasmin 14,5% ($p<0,05$). Probable low-molecular proteinslysis and plasma colagenolyticactivity reduction that correlates with endothelial dys-function symptoms ($r=-0,62$; $p<0,05$) and ($r=-0,56$; $p<0,05$) realtively, and may potentiate vascular wall remodeling has been detected. A probable increase of endothelin-1 (18,8%) has been established, which confirms the leading role of endothelial dysfunction in cardiovascular and pulmonary diseases progression.*

Introduction

Combined course of chronic diseases in humans is a complex modern problem of clinical medicine. Among a number of diseases that affect the adult population, the most common is a combination of coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD), which is from 25,9% to 58% [1]. Global data note that the main cause of death in patients with COPD of medium severity level is a pathology of cardiovascular system (about 50% of mortality), whereas small part of patients (less than 5%) dies from COPD. It has been also is proved the negative impact of COPD on the course of CHD - presence of COPD increases the risk of death in CHD patients by 50%, and decrease of bronchial obstruction indexes as to the influence on the development of coronary catastrophes is compared with hypercholesterolemia [3].

The concept of "cardiovascular continuum", created by V. Dzau and E.Braunwaldin early 90s of the last century which is defined as a set of interconnected pathological processes in the cardiovascular system (hypertension, atherosclerosis and diabetes) and their consequences (myocardial infarction, stroke, heart failure) that develop on a single pathophysiological basis (neuroendocrine dysregulation, endothelial dysfunction, remodeling of heart and blood vessels) is generally used todey. This concept singled out endothelial dysfunction (ED) as one of the main pathogenetical process among a number of the most common cardiovascular diseases [9]. Endothelium provides local hemostasis, maintains tone and structure of blood vessels, ED is one of the earliest atherosclerosis manifestation, exercise tolerance violations, growth factor and atherosclerotic plaque instability, a risk factor of death from cardiovascular causes [2, 8].

There are few data in national literature on the endothelial dysfunction in patients with COPD. Against a background of endothelial dysfunction, especially in combination with coronary heart disease, favorable conditions appear for functional and organic changes of central pulmonary hemodynamics with further remodeling of the left and right heart sections with formation of pulmonary hypertension [4]. These arguments substantiate new direction of fundamental and clinical research - a detailed study of the endothelium participation mechanisms in the pathogenesis of coronary heart disease and COPD.

Aim of the study

To study the relationship of endothelial dysfunction with major pathogenetic changes during combined course of ischemic heart disease and chronic obstructive pulmonary disease.

Materials and methods of the study

To achieve this goal the up-to date biochemical and instrumental methods were used. We examined 113 patients with coronary heart disease: stable exertional angina (SA) II-III functional class(FC). The average age of patients was (56,1 ± 0,76) years, 105 males and 8 females. The disease duration from the moment of making a diagnosis ranged from one to six years. The control group for comparison of the results consisted of 20 healthy individuals matched for age and sex, with no signs of cardiovascular, pulmonological or other internal organs diseases.

Criteria for patients inclusion in the study: based of verified complaints, anamnesis of disease, clinical, instrumental and laboratory studies presence in patient of SA II-III FC and agreement to participate in the research. Criteria for exclusion from the study: chronic heart failure III-IV functional class (NYHA), anamnesis data of stroke suffering, clinically significant arrhythmias and heart conductivity contravention, chronic renal insufficiency, diabetes mellitus, systemic connective tissue diseases and other somatic pathology which are accompanied by changesin studied parameters and can, thus, affect the results of the study.

Inclusion COPD patients in analyzed groups was conducted by screening among people who came to the hospital and were selected randomly according to revenues. Depending on identified changes patients were divided into two groups: the 1st included 63 CHD patients without comorbidity, 2nd - 50 CHD patients with concomitant COPD stage I-II, which corresponded to mild and moderate severity, and at the time the survey was in full remission stage.

The content of endothelin-1 in plasma was determined by immune enzyme test using "Biomedica" reagents kits (Austria). Condition of lipid peroxidation (LPO) was determined by malonic aldehyde levels (MA) in blood by the method of Y. Vladimirova, A.I.Archakova. State of oxidative proteins modification (OPM1) was evaluated by the method of O. Dubininmodificated by I. Meschyshena. Antioxidant status was assessed by parameters of total antioxidant activity (TAA) in blood plasma, catalase activity by M.A.Korolyukamethod et al., and levels of SH-groups, ceruloplasmin (CP) in blood plasma by I.V. Revinamethod. Proteolytic (by lysis of low (LLP) and high proteins (LHB) in blood plasma) and colagenetic blood plasma activity (KAP), total fibrinolytic blood plasma activity (TFA), its enzymatic (TEA) and non-enzymatic (TNA) parts levels were also evaluated.

Mathematical data processing was carried out by using statistical analysis of variations in IBM PC Pentium IV. For most pact of samples at $p<0,05$ values distribution difference from the normal values was set, which is typical for the results of biomedical research. Therefore, the Student t-test was used only when normal distribution for the general equality of variances of compared samples. In other cases, for comparison of the results nonparametric rank test Mann-Whitney was used. The result was considered to be significant if the probability coefficient was equal or less 0,05. Each patient has given written consent for the study in compliance with provisions of the basic GSP (1996), European Convention on Human Rights and Biomedicine (1997), Helsinki Declaration of World Medical Association on ethical principles of scientific medical research involving human (1964 - 2000) and the decree Order of Health Ministry of Ukraine № 281 01.11.2000.

Results

According to our data, of CHD patients without concomitant COPD ET-1 level was 0,39±0,01 fmol/ml and significantly differed with the control group ($p <0,0001$). Initial ET-1 level in blood plasma in CHD patients with COPD amounted to 0,48±0,02 fmol/ml and was significantly higher than in group of comparison ($p <0,0001$). It was established that ET-1 level in blood plasma in CHD patients with concomitant COPD as significantly higher than in the group of persons without comorbidity.

Investigation of pro- and antioxidant processes activity revealed significant difference of each indicator, besides, in CHD patients with COPD these changes were more expressed both by exhaustion of antioxidant protection (AOP) and the strengthening of lipid peroxidation (table 1).

AOP inhibition obviously is caused by increased use of its components to neutralize active radicals and inhibition of free radical oxidation processes of lipids and proteins. From another point of view, both active forms of oxygen and lipid peroxidation products have membranedestructive qualities, disrupt membrane-bound enzyme complexes, cause DNA and RNA damage of as a consequence proteins biosynthesis violation, including antioxidant enzymes.

When studying protease-inhibitory activity of blood plasma we found proteolysis links inhibition both in CHD patients combined with COPD and in CHD patients without comorbidity, however, the presence of COPD significantly reduces low proteins lysis (table 2).

One of these mechanisms changes may be an increase of low-molecular glycoprotein plasma α1-proteinase inhibitor (α1- antitrypsin) activity in blood plasma. Along with inhibition of proteolysis in CHD patients total fibrinolytic activity reduction wasestablished, in CHD patients fibrinolysis decrease is compensated in the early stages by enzymatic activation,

Table 1

Oxidant-antioxidant homeostasis blood plasma indicators in patients with coronary heart disease combined with chronic obstructive pulmonary disease (M ± m, n)

Indexes	Control (n=20)	Group 1 (n=63)	Group 2 (n=50)
TAOApl., %	52,9±0,94	48,5±0,79*	48,7±1,22
CPpl., ml/l	221,6±6,28	318,5±10,28*	378,7±14,98*Δ
SH-groups, mkmol/ml	0,5±0,01	0,34±0,01*	0,3±0,14*
Catalase, mkmol/min	13,7±0,25	10,5±0,23*	9,2±0,17*Δ
MA,mkmol/l	12,8±0,48	19,7±0,30*	22,04±0,24*Δ
OMP,absorb.un./ml	1,29±0,05	1,94±0,06*	2,03±0,06*

Note: * - the probable difference in comparison with the control group (p <0.05);Δ - the probable difference compared to the 1st group (p <0.05)

Table 2

Proteinase-inhibitory blood system indicators in patients with coronary heart disease combined with chronic obstructive pulmonary disease (M ± m)

Indicators	Control (n=10)	Group I (n=30)	Group II (n=25)
LLP, ml/hr	5,23±0,12	3,72±0,03*	3, 57±0,04*Δ
LHP, ml/hr	5,42±0,11	3,84±0,03*	3,80±0,05*
CBA, ml/hr	0,23±0,02	0,16±0,01*	0,11±0,01*Δ
TFA, ml/hr	2,08±0,06	1,59±0,03*	1,64±0,07*
NFA, ml/hr	1,09±0,03	0,78±0,01*	0,84±0,03*
F FA, ml/hr	0,99±0,03	0,81±0,02*	0,81±0,04*

Note: * - difference is probable in comparison with the control group (p<0,05);Δ - difference is probable compared to the 1 group (p <0,05).

whereas the combined course of CHD and COPD these changes are eliminated by non-enzymatic processes.

A correlation analysis Between the level of ET-1 and oxidant-antioxidant homeostasis of blood plasma, fibrinolysis and proteolysis processes was conducted, which revealed the following: direct correlation between the content of ET-1 and OMB (rs=0,6, p <0,05) , ET-1 and CB (rs= 0,5, p <0,05), ET-1 and SH-groups content (rs=0,4, p<0,05) inverse correlation between ET- 1 and azoalbumin lysis (rs=-0,6, p<0,05), between ET-1 and azokol lysis (rs=-0,5, p<0,05), the number of ET-1 and NFA (rs=-0.5, p<0.05).

In many studies [1, 5, 7] combined course of CHD and COPD is treated from a position of mutual encumbrance. Analyzing key pathogenetic shifts we can also state about the formation of vicious circle in progression of comorbid pathology of CHD and COPD. Hypoxia, formed in COPD and its compensatory mechanisms (polycythemia, tachycardia), enhance myocardial oxygen demand in conditions of poor oxygenation of blood and worsening microcirculation. Continuous work of heart in such conditions leads to degenerative changes, accompanied by decrease of myocardium contractile function, which in turn deepens hypoxemia, hypoxia, ventilation-perfusion changes. Hypoxia development promotes increase of pain threshold in corresponding brain centers. These factors combined with the development of pathological changes in myocardium lead to occurrence of silent myocardial ischemia.

Considering the results of the study, endothelial dysfunction can be considered as basic unit of pathogenic transformation that stimulates processes of free radical transformations, depletes antioxidant protection, worsens microcirculation, promotes to cardiovascular and broncho-pulmonary system remodulation, leads to progression of CHD and disorders of pulmonary ventilation destabilization. Revealed violations in such category of patients require appointment of adequately differentiated treatment, which in the early stages of both nosologies will reduce clinical signs and prevent complications.

Conclusions

1.The course of coronary heart disease with concomitant chronic obstructive pulmonary disease is characterized by increased free radical oxidation intensity of lipids by increasing levels of malonic aldehyde 10,1% ($p<0,05$) while reduced antioxidant functioning with catalase activity decrease by 11, 4% ($p<0.05$) and increased of ceruloplasmin levels 14,5% ($p<0,05$).

2.In patients with coronary heart disease combined with chronic obstructive pulmonary disease probable reduction of low protein lysis and low colagenolytic plasma activity was found that correlates with manifestations of endothelial dysfunction ($r=-0,62$; $p<0,05$) and ($r=-0,56$, $p<0,05$) respectively, and may potentiate the vascular wall remodeling.

3.In patients with coronary heart disease combined with chronic obstructive pulmonary disease significant increase of endothelin-1 at 18,8% was found, confirming the leading role of endothelial dysfunction, in the progression of cardiovascular and pulmonary diseases.

Perspectives of further research

Selection of adequate, pathogenetically substantiated treatment will prevent progression of comorbid disorders.

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ВПЛИВ ДИСФУНКЦІЇ ЕНДОТЕЛІЮ НА ОСНОВНІ ПАТОГЕНЕТИЧНІ МЕХАНІЗМИ ПРОГРЕСУВАННЯ ІШЕМІЧНОЇ ХВОРОБИ СЕРЦЯ ПРИ ПОЄДНАННІ З ХРОНІЧНИМ ОБСТРУКТИВНИМ ЗАХВОРЮВАННЯМ ЛЕГЕНЬ

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Резюме. Обстежено 113 хворих на стабільну стенокардію напруження II-III ФК. Визначали рівень ендотеліну-1 у плазмі крові, активність вільнорадикальних процесів та антиоксидантного захисту, протеолізу, фібринолізу. Доведено, що перебіг ішемічної хвороби серця з супутнім хронічним обструктивним захворюванням легень характеризується посиленням інтенсивності процесів вільнорадикального окиснення ліпідів за рахунок збільшення рівня малонового альдегіду на 10,1% ($p<0,05$) при зниженому функціонуванні системи антиоксидантного захисту зі зменшенням активності каталази на 11,4% ($p<0,05$) і збільшенням рівня церулоплазміну на 14,5% ($p<0,05$). Виявлено вірогідне зменшення лізису низькомолекулярних протеїнів і колагенолітичної активності плазми крові, що корелює з проявами ендотеліальної дисфункції ($r=-0,62$; $p<0,05$) і ($r=-0,56$; $p<0,05$) відповідно, та може потенціювати ремоделювання судинної стінки. Встановлено вірогідне зростання рівня ендотеліну-1 на 18,8%, що підтверджує провідну роль ендотеліальної дисфункції в прогресуванні серцево-судинної та легеневої патології.

Ключові слова: ішемічна хвороба серця, ендотелін-1.

ВЛИЯНИЕ ДИСФУНКЦИИ ЭНДОТЕЛИЯ НА ОСНОВНЫЕ ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ПРОГРЕССИРОВАНИЯ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА ПРИ СОЧЕТАНИИ С ХОБЛ

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Резюме. Обследовано 113 больных со стабильной стенокардией напряжения II-III ФК. Определяли уровень эндотелина-1 в плазме крови, активность свободнорадикальных процессов и антиоксидантной защиты, протеолиза, фибринолиза. Доказано, что течение ишемической болезни сердца с сопутствующей хронической обструктивной болезнью легких характеризуется усилением интенсивности процессов свободнорадикального окисления липидов за счет увеличения уровня малонового альдегида на 10,1% ($p<0,05$) при пониженном функционировании системы антиоксидантной защиты с уменьшением активности каталазы на 11 4% ($p<0,05$) и увеличением уровня церулоплазмина на 14,5% ($p<0,05$). Выявлено достоверное уменьшение лизиса низкомолекулярных протеинов и колагенолитической активности плазмы крови, которое коррелирует с проявлениями эндотелиальной дисфункции ($r=-0,62$; $p<0,05$) и ($r=-0,56$; $p<0,05$) соответственно, и может усиливать ремоделирование сосудистой стенки. Установлено достоверное повышение уровня эндотелина-1 на 18,8%, что подтверждает ведущую роль эндотелиальной дисфункции в прогрессировании сердечно-сосудистой и легочной патологии.

Ключевые слова: ишемическая болезнь сердца, эндотелин-1.

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