



THE PECULIARITIES OF THE CHANGES OF SOME CARDIOHEMODYNAMIC AND MICROCIRCULATORY INDICES IN CONDITIONS OF THE COMORBID COURSE OF ESSENTIAL HYPERTENSION

BURMAK YU.G.*, PETROV YE.YE., KAZAKOV YU.M., CHEKALINA N.I., TREUMOVA S.I.,
TRIBRAT T.A., IVANITSKAYA T.A., KOZLENKO T.V.

Department of Propaedeutics to Internal Medicine with Care of Patients, General Practice (Family Medicine),
Medicine Faculty 1, Ukrainian Medical Stomatological Academy, Poltava, Ukraine

Received 08.09.2019; accepted for printing 25.04.2020

ABSTRACT

The peculiarities of cardiohemodynamics, microcirculation, and microvasculature are presented in the article; their correlation with significance of the oxidative stress, the level of antioxidative blood potential and endothelial function in the isolated course of essential hypertension and in conditions of its comorbidity with duodenal peptic ulcer was carried out. It was established that the presence of the remodeling left ventricle with the unchanged contractile function, and maximal intensity of both resistivity of the peripheral vascular system ($p < 0.001$), and disorders of microcirculation and microvasculature on the perivascular, vascular, and intravascular levels ($p < 0.001$) is typical of the patients with the comorbid course of essential hypertension. The next results showed that manifestations of oxidative stress were the most significant ($p < 0.001$) among the patients with the combinative pathology. The index of the antioxidative ability of blood serum was low in these patients ($p < 0.001$), besides, it had the negative correlation relationship with the index of the total changes of microhemocirculation and microvasculature ($r = -0.467$; $p < 0.05$). At the same time the index of ristomycin-induced platelet aggregation as reflection of the changed endothelial function and a marker of the thrombogenic risk was also the highest in case of the comorbid course of essential hypertension ($p < 0.001$). Besides that, its positive correlation relationship with the index of the total changes of microhemocirculation and microvasculature ($r = +0.465$; $p < 0.05$) was established.

Thus, the significant increase of resistivity of the peripheral part of the vascular system with the presence of the significant changes of microcirculation and microvasculature is a typical peculiarity of cardiohemodynamics' changes in the patients with the comorbid course of essential hypertension with the unchanged contractile function of myocardium of the left ventricle in conditions of its remodeling. Their connection with intensity of the oxidative stress and the endothelial dysfunction reflects a pathogenetic community of the vascular changes' forming and determines their as a factor of aggravation of the essential hypertension course in conditions of comorbidity.

KEYWORDS: Essential hypertension, comorbidity, cardiohemodynamics, microcirculation, lipid peroxidation, endothelial dysfunction.

INTRODUCTION

Essential hypertension and duodenal peptic ulcer is an important medical and social problem despite the new epidemiological data and the results of the clinical studies, which completed representations about mechanisms of their forming

and changed approaches to their treatment.

While figuring out the development mechanisms of "mutual aggravation syndrome" in the comorbid pathology [Boyd C, 2005; Sharabichiev Yu et al., 2014; Shirinsky V et al., 2014; Gubanova G et al., 2015] the researchers paid their attention to disregulatory processes and metabolic changes observed among the patients in conditions of combined pathology. In particular, the role of hypoxia in the cardiovascular system pathology resulted to the decrease of bioenergetical processes, the increase of

ADDRESS FOR CORRESPONDENCE:

Yu.G.Burmak
Ukrainian Medical Stomatological Academy
23 Shevchenko Street, Poltava 36000, Ukraine
Tel.: (+38) 050-907-76-20, (+38) 098-332-88-19
E-mail: yu.burmak@gmail.com

the forming of the active oxygen forms and the activation of lipid peroxidation process [Giordano F, 2005; Chekman I et al., 2008; Gonchar O et al., 2017; Mičova P et al., 2017; Münzel Th et al., 2017] was noted. The importance of lipid peroxidation processes as a leading link in the peptic ulcer genesis was also established. Besides, the ability of the lipid peroxidation products to form the changes of microvasculature vessels and microhemodynamics was noted. It was accompanied by the trophic disorder, hypoxia of the mucous membrane of the stomach and duodenum [Demir S et al., 2003; Kaur A et al., 2012; Liu L et al., 2013; Kolotilova M et al., 2014; Minayan M et al., 2018].

The morpho-functional condition of the vessels and nitrogen oxide have a great importance in the pathology's genesis as endothelium is the tissue which produces factors of multidirectional action and endothelial dysfunction with chronic low-level systemic inflammation play a great role in the EHT pathogenesis. It was noted that activated proinflammatory factors with the following affection of the vascular endothelium can be a result of the hemodynamic stress which accompanies the atherogenic process [Harrison D et al., 2011; Rajendran P et al., 2011; Tuev A et al., 2011; Vasilets L et al., 2012; Dinh Q et al., 2014; Statsenko M et al., 2018]. The change of the vascular viscoelasticity properties is one of the significant manifestations of the vessels' affections. An early decrease of distensibility and elasticity of the great vessels with an unfavorable prognostic value is noted in EHT [Nazarova O et al., 2012; Otteeva E et al., 2012;

Logacheva O et al., 2013; Ecobici M, Iliesku E, 2017; Safar M et al., 2018]. The researchers have noted an importance and a role of hemodynamic and neuro-humoral factors of a pressor and growth character. It was established that the disease with the increase of periph-

eral vascular resistance caused first of all by the increase of the resistive vessels tonus with following remodeling of the heart and vessels is one of the severe variants of the EHT course. It was also noted that oxidative stress can result in worsening of endothelium-dependent vasodilation due to the increase of nitrogen oxide inactivation. Besides, a significant decrease of the nitrogen oxide production can be a result of EHT [Topchiy I, 2007; Mayanskaya S et al., 2009; Gönenç A et al., 2013; Mel'nikova Yu et al., 2015]. It was also noted that it is not the only mechanism of the EHT forming taking into account a possibility of the secondary endothelial dysfunction in relation to the vascular remodeling.

It is necessary to mention that endothelial dysfunction occurs not only in the cardiovascular system pathology, but also in conditions of the digestive system pathology [Oparin A et al., 2002; Osadchuk M et al., 2005; Panova I et al., 2012; Shankar V et al., 2012; Oparin A et al., 2013; Kaniovska L et al., 2016] besides, this process is generalized, and it worsens the functional and protective properties of the mucous membrane of the gastrointestinal tract. It is interesting to note that activity of Willebrand factor as the marker of endothelial dysfunction among the patients with peptic ulcer was caused significantly by the presence of Helicobacter pylori antibodies. In this connection endothelial dysfunction wasn't considered only as one of the mechanisms of its negative influence upon the protective mucous barrier of the stomach but also as one of the potential mechanisms of the complicated course of EHT.

We noted the change of the endothelial function and metabolic indices in the patients with the comorbid course of EHT too [Burmak Yu et al., 2017]. Besides, taking into account the foregoing we assumed the presence of the peculiarities of the hemodynamic and microcirculatory changes in such patients and it was a ground for carrying out this work.

The aim of the study was to reveal peculiarities of cardiohemodynamics, microcirculation and microvasculature, find their connection with the changed antioxidative blood potential and endo-



To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

thelial function and to establish their role as a factor of worsening of the EHT course in conditions of comorbidity with duodenal peptic ulcer.

MATERIAL AND METHODS

Totally 68 patients (35 males and 33 females) with essential hypertension of II stage (medicamentous control) were examined. Among them its course was isolated in 33 patients (the comparative group) and 35 patients (the main group) had EHT combined with duodenal peptic ulcer (the remission phase). The mean age of the patients was 44.4 ± 2.8 years. The reference indices were obtained in 23 practically healthy individuals. They and the examined patients were of the same sex and age.

The study of structural-functional indices of myocardium and cardiohemodynamics was carried out by means of echocardiography (Siemens 1-M, Germany). The following indices were calculated and estimated: sizes of the right ventricle and the left atrium, diameter of the aorta, thickness of the posterior wall of the left ventricle (PWLV_D) and the interventricular septum (IVS_D), the end-systolic and the end-diastolic dimensions of the left ventricle (ESD_{LV} and EDD_{LV}, accordingly), the end-systolic and the end-diastolic volumes of the left ventricle (ESV_{LV} and EDV_{LV}, accordingly), the stroke volume, cardiac output, stroke index and the cardiac index, the ejection fraction of the left ventricle and the total peripheral vascular resistance (TPVR).

The study and the analysis of the microhemocirculation and microvasculature condition were conducted by biomicroscopy of bulbar conjunctiva (BBC) by means of a slit lamp "SL-2B" ("ZOMZ", Russian Federation) with calculation of conjunctival indices (CNI) on the perivascular (CNI_{PV}), vascular (CNI_V), intravascular (CNI_{IV}) levels and the index of the total changes (CNI_T), intravascular aggregation of hemocytes was studied with revealing phenomenon.

The content of the intermediate (diene conjugates – DC) and the final (malondialdehyde - MDA) products of lipid peroxidation, activity of enzymes of antioxidant protection system (catalase and superoxide dismutase in the blood erythrocytes) were studied by means of spectrophotometry, the integral index of the antioxidative ability of blood serum

(IIAABS) was calculated as a correlation of the product of key enzymes of antioxidant protection (superoxide dismutase x catalase) to the final product of lipid peroxidation (MDA), a tissue component of the primary hemostasis was estimated by means of spectrophotometry by ristomycin-induced platelet aggregation (RIPA).

Statistical proceeding of the results was carried out using the license programs packages Microsoft Office 97, Microsoft Excel Stadia 6.1/ prof and Statistica.

RESULTS AND DISCUSSION

During the study of structural-functional indices of myocardium and systemic hemodynamics (Table 1) it was revealed that patients with the comorbid course of EHT (the main group) had hypertrophy of the myocardium of the left ventricle. PWLV_D and IVS_D were increased in comparison with the indices of reference norm (accordingly, in 1.5 and 1.8 times;

TABLE 1

Peculiarities of structural-functional indices of myocardium and systemic hemodynamics in the patients with isolated and comorbid course of EHT

Indices	Practically healthy individuals (n = 23)	Patients with EHT (n = 33)	Patients with EHT(+) (n = 35)
RV(mm)	25.5±0.2	28.6±0.3*	28.0±0.3*
AO(mm)	28.5±0.4	29.6±0.6	30.3±0.7
LA(mm)	28.4±0.4	33.1±0.5*	35.7±0.3* ^x
IVS _D (mm)	7.11±0.4	11.2±0.6*	12.7±0.7*
PWLV _D (mm)	8.79±0.5	12.7±0.6*	13.5±0.7*
EDD _{LV} (mm)	50.5±0.2	55.1±0.3*	56.7±0.2* ^x
ESD _{LV} (mm)	33.3±0.2	38.4±0.2*	40.2±0.2* ^x
EDV _{LV} (ml)	113.1±5.5	123.6±6.8	129.3±5.3
ESV _{LV} (ml)	47.4±5.1	56.3±5.7	57.2±4.5
EF(%)	60.2±2.3	55.7±2.6	55.8±2.5
SV(ml)	65.1±5.2	69.1±4.6	71.3±5.3
SI(ml/m ²)	37.7±2.8	40.1±2.6	41.8±2.1
CO(l/min)	4.93±0.41	5.39±0.44	5.63±0.42
CI(l/min/m ²)	2.89±0.32	3.21±0.26	3.32±0.29
TPVR (dyne·cm ⁻⁵ ·s)	1921.3±33.9	2361.1±33.4*	2685.4±51.1* ^x

NOTE: ENT(+) - Patients with EHT in combination with duodenal peptic ulcer, significance of differences with reference results: * - $p < 0.001$; significance of differences between groups of the patients: ^x - $p < 0.001$

$p < 0.001$ in both cases) and exceeded the borders of physiological parameters [Lang R et al., 2006]. Besides, a significant enlargement of the left chambers was revealed in these patients in comparison with the reference norm: left atrium – in 1.26 times ($p < 0.001$), left ventricle (an increase of ESD_{LV} and EDD_{LV} in 1.12 and 1.21 times, accordingly; $p < 0.001$). Besides, the presence of increased of the ESV_{LV} and EDV_{LV} ($p > 0.05$) had no impact on the contractile myocardial function and EF of the left ventricle wasn't changed significantly. The revealed peculiarities must have been the result of compensatory mechanisms and the reflection of processes of myocardial remodeling in conditions of arterial hypertension [Yevtyukhin I et al., 2017]. At the same time, a significant increase of TPVR was revealed in the patients with the comorbid course of EHT, besides, this index was 1.4 times as high as one among practically healthy individuals ($p < 0.001$). One should note that the sizes of the left chambers (LA, ESD_{LV} , EDD_{LV}) in the patients of the main group were also significantly increased ($p < 0.001$) in comparison with the patients of the comparative group, and TPVR in the patients with EHT in comorbidity conditions exceeded TPVR in the patients with isolated course of EHT in 1.14 times ($p < 0.001$).

The same changes of TPVR in the patients with comorbid pathology were noted by Surmylo N.N. and co-authors (2018), but we, as distinct from them, didn't reveal a connection of this index with other parameters of hemodynamics. The foregoing was a proof of the more significant morphofunctional myocardial changes and reflected the presence of an independent prognosis-negative factor of the cardiovascular morbidity and mortality [Shelest B, 2016] in the patients with the comorbid pathology. Resistivity of the peripheral part of the vascular system was the most significant in these patients. It was a precondition for the following study of the condition of microhemocirculation and microvasculature.

Table 2 demonstrates the significant changes of microvasculature on the perivascular level in the patients with the comorbid course of EHT (CNI_{PV} was increased in 17.6 times in comparison with the reference norm – perivascular edema, simple hemorrhages, pigmented spots were diagnosed) and

changes on the vascular and intravascular levels were also significant (an increase of CNI_V and CNI_{IV} in 2.05 and 9.17 times, accordingly). It was revealed that inequality of caliber, microvascular tortuosity and polymorphism, decrease of arteriovenular coefficient to 1:4-1:6 (in practically healthy individuals its result was 1:2-1:3), reduction of capillary net and an increase of functioning arteriovenular shunts were the main changes on the vascular level. Meandrous tortuosity of the veins, venular sacculations were diagnosed in 30 patients with comorbid pathology (85.7%) (in the comparative group – 21 cases, or 63.6%). The presence of microaneurysms among the patients of the main group was revealed in 21 patients (60% cases), whereas among patients of the comparative group – only in 17 cases (51.5%). A slow blood flow, a retrograde blood flow, the stasis of the blood in capillaries and some arterioles, aggregation of erythrocytes, in venules- with the presence of slage-syndrome of the II degree – were the main changes on the intravascular level in the patients with the comorbid course of EHT. A significant increase of CNI_T in comparison with the reference norm (in 3.7 times; $p < 0.001$) was caused by the foregoing changes of microvasculature on the perivascular, vascular, and intravascular levels. It is necessary to note that the significance of the

TABLE 2
Peculiarities of indices of microhemocirculation and microvasculature in the patients with isolated and comorbid course of EHT

Indices	Practically healthy individuals (n = 23)	Patients with EHT (n = 33)	Patients with EHT (+) (n = 35)
CNI_{PV}	0.08±0.05	0.62±0.14*	1.41±0.16*. ^x
CNI_V	2.28±0.15	3.26±0.15*	4.69±0.22*. ^x
CNI_{IV}	0.47±0.04	1.41±0.14*	4.31±0.18*. ^x
CNI_T	2.84±0.21	5.38±0.23*	10.52±0.28*. ^x

NOTE: ENT(+) - Patients with EHT in combination with duodenal peptic ulcer; significance of differences with reference results: * - $p < 0.001$; significance of differences between groups of the patients: ,^{xxx} - $p < 0.001$

changes of indices CNI_{PV} , CNI_V , CNI_{IV} , and CNI_T in the patients with EHT in combination with duodenal peptic ulcer exceeded the same indices in the patients with the isolated course of EHT (in 2.2, 1.3, 3 and 2 times, accordingly; $p < 0.001$ in all cases).

It reflected the most significant changes of microhemodynamics and microvasculature in the patients with EHT in conditions of comorbidity; it was also mentioned by Shelest B.A. and co-authors (2018).

Some authors have mentioned the changes of microhemocirculation and microvasculature in the patients with EHT [Kirichenko A, Averyanova I, 2012; Pries A, 2014; Kvasnikov A et al., 2018]. They have emphasized an important role of the changes of systemic circulation (an increase of cardiac ejection), central controlling mechanisms and the endothelial reaction in microvessels for forming of the foregoing.

The role of disorders of the regional blood flow and microcirculation in the process of ulcerogenesis was shown by Akermi J. and Andreeva Y. (2013) and Zatorsky H. (2017); besides, the influence of vasodilators produced by endothelial cells upon the development of microcirculatory changes was accentuated. It is interesting to note that the pathogenetically grounded treatment of the patients both with EHT and peptic ulcer promoted the diminishing of microcirculatory disorders [Kirichenko A et al., 2012; Akermi J, Andreeva Y, 2013].

Taking into account the general clinical importance of the prooxidant-antioxidant balance both inprotective mechanisms and formation of the internal organs' pathology, the study of the content of intermediate (DC), final (MDA) products of lipid peroxidation and key enzymes of antioxidant protection system (superoxide dismutase, catalase) in the blood of the patients with the comorbid course of EHT was our following step. Besides, a significant increase of activity of lipid peroxidation processes in the patients with the comorbid course of EHT was revealed. It was shown by an increase of diene conjugates (17.91 ± 0.32 $mcmol/l$) and MDA (6.59 ± 0.29 $mcmol/l$) content in comparison with the reference norm, accordingly, in 1.9 times (9.21 ± 0.09 $mcmol/l$; $p < 0.001$) and in 2 times (3.23 ± 0.06 $mcmol/l$; $p < 0.001$). It is necessary to

mention that an increase of diene conjugates (in 1.5 times) and MDA (in 1.6 times) in the patients of the main group was also noted in comparison with the patients with the isolated course of EHT (11.86 ± 0.23 $mcmol/l$ and 4.12 ± 0.25 $mcmol/l$, accordingly; $p < 0.001$). The obtained results corresponded to the information from available literature about the role of the oxidative stress in the realization of the arterial hypertension [Rajendram P et al., 2013; Vlasenko EM, 2015] and ulcerogenesis [Demir S et al., 2003; Kaur A et al., 2012] mechanisms. Besides, the authors have emphasized the importance of antioxidant protection systems for leveling of oxygen's active forms. During the study of a content of the key enzymes of antioxidant protection – superoxide dismutase and catalase - their downdrift was revealed (25.3 ± 1.8 $MU/mgHb$ и 311.9 ± 10.6 $MU/mg Hb$, accordingly). But dynamics of the change of the lipid peroxidation indices and enzymes of antioxidant protection was the following: IIAABS was more than 2.2 times as little as IIAABS among practically healthy individuals (1363.8 ± 22.3 to 3065.1 ± 38.7 ; $p < 0.001$) and more than 1,6 times as little as among the patients of the comparative group (2257.4 ± 25.6 ; $p < 0.001$). It was a reflection of the functional exhaustion of an enzymatic link of the antioxidant protection system. It is necessary to emphasize the negative correlation relationship between IIAABS and CNI_T ($r = -0.467$; $p < 0.05$). It reflects participation of lipoperoxid homeostasis' disorders in the formation of the changes of microvasculature and microhemocirculation. During the following study of the functional condition of the vascular-platelet link of the primary hemostasis we didn't reveal any significant changes in the indices of the functional tests but a significant increase of RIPA as an index of the high thrombogenic risk [Voznyuk L et al., 2012; Gomellya M, 2014] was revealed. Besides, its value in the patients with the comorbid course of EHT ($136.6 \pm 4.5\%$) exceeded the reference result ($94.06 \pm 2.11\%$; $p < 0.001$) in 1.45 times and the analogous index of the comparative group ($123.3 \pm 2.61\%$; $p < 0.05$) in 1.11 times. The revealed positive correlation relationship between RIPA and CNI_T ($r = +0.465$; $p < 0.05$) directed totally to their

community in the mechanisms of the development of the microhemocirculation's and microvasculature changes.

Thus, the study and the analysis of cardiohemodynamics, microhemodynamics and microvasculature, of the content of lipoperoxidation products, the activity of enzymes of antioxidant protection and estimation of the tissue component of the primary hemostasis in the patients with comorbid duodenal peptic ulcer gave us an opportunity to establish a number of peculiarities presented below.

CONCLUSION

The significant increase of resistivity of the peripheral part of the vascular system (TPVR) with the presence of the significant changes of micro-

circulation and microvasculature totally (CNI_T) is a typical peculiarity of cardiohemodynamic's changes in the patients with the comorbid course of EHT with the unchanged contractile function of myocardium of the left ventricle (EF) in conditions of its remodeling. The directed changes are accompanied by a significant activation of lipid peroxidation processes (DC, MDA), a decrease of the antioxidative blood potential (IIAABS) and a significant increase of the thrombogenic complications risk (RIPA). The established direct and inverse correlation relationship between the indices CNI_T , IIAABS and RIPA reflects their pathogenic community in the formation of the vascular changes and determine them as a factor of aggravating the comorbid course of EHT.

ABBREVIATIONS

AO - diameter of the aorta
 BBC - biomicroscopy of bulbar conjunctiva
 CNI - conjunctival indices
 CNI_{IV} - intravascular conjunctival indices
 CNI_{PV} - perivascular conjunctival indices,
 CNI_T - total conjunctival indices
 CNI_V - vascular conjunctival indices
 CO - cardiac output
 CT - catalase
 DC - diene conjugates
 EDD_{LV} - end-diastolic dimensions of the left ventricle
 EDV_{LV} - end-diastolic volumes of the left ventricle
 EF - ejection fraction

EHT - Essential hypertension
 ESD_{LV} - end-systolic dimensions of the left ventricle
 ESV_{LV} - end-systolic a volumes of the left ventricle
 IIAABS - integral index of the antioxidative ability of blood serum
 IVS_D - interventricular septum,
 LA - left atrium
 MDA - malondialdehyde
 $PWLVD$ - posterior wall of the left ventricle
 RIPA - ristomycin-induced platelet aggregation
 RV - right ventricle
 SI - stroke index
 SV - stroke volume
 TPVR - total peripheral vascular resistance.

REFERENCES

1. *Akermi J, Andreeva YA.* Gastric mucosal microcirculation in patients with duodenal peptic ulcer against the background of eradication therapy. *Journal of V.N. Karazin' KhNU.* 2013; 1044: 8-12
2. *Gonchar OA, Mancovska IN.* Time-depend effect of severe hypoxia/reoxygenation on oxidative stress level, antioxidant capacity and p53 accumulation in mitochondria of rat heart. *The Ukrainian Biochemical Journal.* 2017;89(6): 39-47. DOI: 10.15407/ubj89.06.039
3. *Boyd CM, Darer C, Boulton C., et al.* Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implication for performance. *JAMA.* 2005; 294(6): 716-724. DOI: 10.1001/jama.294.6.716
4. *Burmak YuG, Kazakov YuM, Treumova SI., et al.* Changes of some immune and metabolic indices as burdening criterion of chronic systemic inflammation in essential hypertension comorbidity. *The New Armenian Medical Journal.* 2017; 11(2): 20-26
5. *Chekman IS, Dachyk NO, Lukunova OM, Zagorodnyy MI.* [The role of lipid peroxidation in pathogenesis of arterial hypertension] [Published in Ukrainian]. *Medicine of Ukraine.* 2008; 6(122): 76-81
6. *Demir S, Yilmaz M, Köseoglu M., et al.* Role of free radicals in peptic ulcer and gastritis. *The Turkish Journal of Gastroenterology.* 2003; 14(1): 39-43
7. *Dinh QN, Drummond GR, Sobey ChG, Chrisobolis S.* Roles of Inflammation, Oxidative Stress, and Vascular Dysfunction in Hyperten-

- sion. *BioMed Research International*. 2014; 2014, Article ID 406960: 11 pages. DOI: 10.1155/2014/406960
8. *Ecobici M, Iliesku EL*. Arterial Stiffness and Hypertension – Which Comes First? *Maedica (Buchar)*. 2017; 12(3): 184-190
9. *Giordano FJ*. Oxygen, oxidative stress, hypoxia, and heart failure. *The Journal of Clinical Investigation*. 2005; 115(3): 500-508. DOI: 10.1172/JCI24408
10. *Gomellya MV*. [Investigation of ristocetin-induced platelet aggregation, parameters of von Willebrand factor and the coagulation factor VIII at essential arterial hypertension in children] [Published in Russian]. *Bulletin of East Siberian Scientific Center SB RAMS*. 2014; 1(95): 14-17
11. *Gönenç A, Hacısevski A, Tavil Yu, Torun M*. Oxidative stress in patient with essential hypertension: A comparison of dippers and non-dippers. *European Journal of Internal Medicine*. March 2013; 24(2): 139-144. DOI: 10.1016/j.ejim.2012.08.016
12. *Gubanova GV, Belyaeva JN, Shemetova GN*. [Multimorbidity patient: stages of formation, risk factors and management tactics] [Published in Russian]. *Modern Problems of Science and Education*. 2015; 6p. URL: <http://www.science-education.ru/ru/article/view?id=23986>
13. *Harrison DG, Guzik TJ, Lob H., et al*. Inflammation, Immunity and Hypertension. *Hypertension*. 2011; 57(2): 132-140. DOI: 10.1161/HYPERTENSIONAHA.110.163576
14. *Kaniovska LV, Kaushanska OV, Bedyk NM, Novytska IO*. [*Helicobacter pylori* as a topical problem of modern gastroenterology (Literary review)] [Published in Ukrainian]. *Young Scientist*. 2016; 2(29): 156-160
15. *Kaur K, Singh R, Sharma R, Kumar S*. Peptic ulcer: a review on etiology and pathogenesis. *International Research Journal of Pharmacy*. 2012; 3(6): 34-38
16. *Kirichenko AA, Averyanova IM*. [Microcirculation in arterial hypertension: effect of blood pressure control with antihypertensive therapy] [Published in Russian]. *Russian Journal of Cardiology*. 2012; 3 (95): 38-41
17. *Kolotilova ML, Ivanov LN*. [Neurosis and Genetic Theory of Etiology and Pathogenesis of Ulcer Disease] [Published in Russian]. *Annals of the Russian Academy of Medical Sciences*. 2014; 7-8: 10-16. DOI: 10.15690/vramn.v69i7-8.1104
18. *Kvasnikov A, Podzolkov V, Bragina A., et al*. Macro- and microcirculatory abnormalities of vascular wall in hypertensive patients. *Journal of Hypertension*. 2018; 36, e-Supplement 1: e284. DOI: 10.1097/01.hjh.0000539826.76028.0b
19. *Liu L, Liu Ya, Cui J., et al*. Oxidative stress induces gastric submucosal arteriolar dysfunction. *World Journal of Gastroenterology*. 2013; 19(48): 9439-9446. DOI: 10.3748/wjg.v19.i48.9439
20. *Logacheva OS, Kozhevnikova OV, Paltseva AE, Namazova-Baranova LS*. [Modern Methods of Identifying the predictors of Cardio-Vascular Diseases in Children at Early Stages] [Published in Russian]. *Pediatric Pharmacology*. 2013; 10(2): 117-120. DOI: 10.15690/pf.v10i2.653
21. *Lung MR, Bierig M, Devereux RB., et al*. Recommendations for Chamber Quantifications. *European Journal of Echocardiography*. 2006; 7: 79-108. DOI: 10.1016/j.euje.2005.12.014
22. *Mayanskaya SD, Popova AA, Mayanskaya NN., et al*. [Arterial hypertension and endothelium dysfunction] [Published in Russian]. *The Bulletin of Contemporary Clinical Medicine*. 2009; 2(3): 43-48
23. *Mel'nikova YuS, Makarova TP*. [Endothelial dysfunction as the key link of chronic diseases pathogenesis] [Published in Russian]. *Kazan Medical Journal*. 2015; 96(4): 659-665. DOI: 10.17750/KMJ2015-659
24. *Mičova P, Klevstig M, Holzerová K., et al*. Antioxidant tempol suppresses heart cytosolic phospholipase A2 α stimulated by chronic intermittent hypoxia. *Canadian Journal of Physiology and Pharmacology*. 2017; 95(8): 920-927. DOI: 10.1139/cjpp-2017-0022

25. Minayan M, Sajjadi SE, Amini K. Antiulcer effects of *Zataria multiflora* Boiss. on indomethacin-induced gastric ulcers in rats. *Avicenna Journal of Phytomedicine*. 2018; 18(5): 408-415
26. Münzel Th, Giovanni GC, Maack Ch., et al. Impact of Oxidative Stress on the Heart and Vasculature. *Journal of the American College of Cardiology*. 2017; 70(2): 212-229. DOI: 10.1016/j.jacc.2017.05.035
27. Nazarova OA, Nazarov AV. [Vascular lesion in arterial hypertension][Published in Russian] *Bulletin of the Ivanovo state medical academy*. 2012; 17 (2): 60-66.
28. Oparin AA, Dvoyashkina J, Khomenko I. [Features of endothelial dysfunction and vegetation of dystonia at duodenal ulcer for students] [Published in Russian]. *World of Medicine and Biology*. 2013; 3: 44-46
29. Oparin AG, Oparin AA. [Endothelial dysfunction in pathogenesis of duodenal ulcer] [Published in Russian]. *Clinical Medicine*. 2002; 80(1): 53-54
30. Osadchuk MA, Kulidzhanov AYu. [Melatonin-producing and NO-synthesis positive gastric cell and the process of cellular renewal in gastric and duodenal ulcer] [Published in Russian]. *Clinical Medicine*. 2005; 9: 34-37
31. Otteeva EN, Klinkova EV, Garbuzova OG., et al. [Arterial rigidity, a marker of cardiovascular diseases] [Published in Russian] *Clinical Medicine*. 2012; 1: 4-12
32. Panova IV, Dudnikova EV. [Nitric oxide and endothelin-1 in children with digestive disorders] [Published in Russian]. *Current Pediatrics*. 2012; 11(5): 56-62. DOI: 10.15690/vsp.v11i5.429
33. Pries AR. Microcirculation in hypertension and cardiovascular disease. *European Heart Journal, Supplements*. 2014; 16(Supplement A): A28-A29. DOI: 10.1093/eurheartj/sut007
34. Rajendran P, Rengarajan T, Thangarel J., et al. The Vascular Endothelium and Human Diseases. *International Journal of Biological Sciences*. 2013; 9(10): 1057-1069. DOI: 10.7150/ijbs.7502
35. Safar ME, Asmar R, Benetos A., et al. Interaction between hypertension and arterial stiffness. an expert reappraisal. *hypertension*. 2018; 72(4): 796-805. DOI: 10.1161/HYPERTENSIONAHA.118.11212
36. Shankar V, Kutty AVM, Annamalai N. Helicobacter pylori infection and hypertension: Is there association? *Biomed Res – India*. 2012; 23(4): 537-539
37. Sharabichiev YuT, Antipov VV, Antipova SI. [Comorbidity is an actual scientific and practical problem of 21st century medicine] [Published in Russian]. *Meditcinskie Novosti*. 2014; 8: 6-11
38. Shelest BA. [Peculiarities of cardiac hemodynamics in hypertensive patients with comorbid pathology] [Published in Russian]. *Experimental and Clinical Medicine*. 2016; 72: 69-73
39. Shirinsky VS, Shirinsky IV. [Comorbid diseases as an important problem of clinical medicine] [Published in Russian]. *The Siberian Medical Journal*. 2014; 29(1): 7-12. DOI: 10.29001/2073-8552-2014-29-1-7-12
40. Statsenko ME, Derevyanchenko MV. [The role of systemic inflammation in decrease of elasticity of magistral arteries and in progression of endothelial dysfunction in patients with systemic hypertension, obesity and type 2 diabetes] [Published in Russian]. *Russian Journal of Cardiology*. 2018; 4(156): 32-36. DOI: 10.15829/1560-4071-2018-4-32-36
41. Surmylo NN, Kovaliova OV. [Correction of microcirculation disorders in diseases of digestion organs of professional etiology in the rehabilitation period in multimorbid patients] [Published in Ukrainian]. *Medical perspectives*. 2018; tom XXXIII, #3 (part 1): 202-209. DOI: 10.26641/2307-0404.2018.3(part1).142381
42. Topchiy II. [Oxidative stress, increase of level dimethylarginine and uncoupled nitric oxide synthases as risk factors of arterial hypertension and chronic renal disease] [Published in Russian]. *Ukrainian Therapeutical Journal*. 2007; 3: 8-14

43. Tuev AV, Karpunina NS. [Inflammatory markers in essential hypertension and coronary artery disease: clinical and predictive value] [Published in Russian]. *Arterial Hypertension*. 2011; 17(6): 550-554. DOI: 10.18705/1607-419X-2011-17-6-550-554
44. Vasilets LM, Grigoriadi NE, Gordiyuchuk RN, et al. [The features of the inflammation indicators in the group of the patients with the arterial hypertension] [Published in Russian]. *Modern Problems of Science and Education*. 2012; 6 pages. URL: <http://www.science-education.ru/ru/article/view?id=7539>
45. Vlasenko EM. [Relationship between daily blood pressure profile and a marker of chronic systemic inflammation in patients with stage 2 essential hypertension with microalbuminuria] [Published in Russian]. *International Medical Journal*. 2015; 2: 29-33
46. Voznyuk LA, Pivtirak KV, Semenenko SI. [vWF Factor As A Criterion Of Inflammation And Endothelial Dysfunction, Coronary Artery Disease In the Patients With Ischemic Heart Diseases] [Published in Ukrainian]. *Bulletin of problems in biology and medicine*. 2012; 1(92): 39-42
47. Yevtyukhin IYu, Dedov PV, Mazayev VP, et al. [Myocardium remodeling and the risk of cardiovascular complications with patients with ischemic heart disease and arterial hypertension] [Published in Russian]. *Modern problems of science and education*. 2017; 6p. URL: <http://www.science-education.ru/ru/article/view?id=27173>
48. Zatorsky H. *Pathophysiology and Risk Factors in Peptic Ulcer Disease. Introduction to Gastrointestinal Diseases*: Ed. by J. Finna. 2017; 2: 9-11
-
-