

ROLE OF HYPERCORTISOLEMIA IN THE COMORBID COURSE OF CORONARY ARTERY DISEASE, DIABETES MELLITUS TYPE 2 AND ANEMIA*N.D. Pavliukovych, O.V. Pavliukovych, V.O. Shuper, O.V. Zaliavska*

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XXIV.3.95.2020.74**E-mail:**
natasha.pavliukovych@gmail.com**Abstract.** The results of the investigation are components of the scientific-research work “Features of the comorbid course of the diseases of internal organs: risk factors, mechanisms of the progression and comorbidity, pharmacotherapy”. №0114U002475. The aim of the study – investigation of dynamics of cortisol synthesis changes in patients of older age groups with coronary artery disease (CAD) with comorbid diabetes mellitus type 2 (DM) and anemic syndrome (AS).**Material and methods.** Blood cortisol level was measured in 40 old and senile CAD patients with comorbid DM and AS of different degrees of severity. Control group consisted of 12 patients with CAD without comorbidities that were not significantly different by gender and age from patients of research groups. Possible effects of telmisartan on the degree of chronic hypoxia were also investigated.**Results.** In patients of old and senile age with CAD and comorbid AS, same as in case of CAD and AS on the background of DM, activation of the cortisol synthesis is observed, likely in response to hypoxia as a stress factor in anemia. The degree of severity of the detected changes was different depending on the degree of anemia severity. There was no normalization of cortisol content in blood in any of the major experimental groups regardless the prescribed treatment with ACE inhibitors or telmisartan.**Conclusion.** In patients with CAD, same in the case of a comorbid course of CAD and DM, an increase of cortisol secretion in response to anemic hypoxia was observed. As the degree of severity of the AS progressed, gradual decreasing of cortisol blood level was detected. Reduction of the intensity of stress-limiting systems in the organism by telmisartan prescription may help to eliminate the adverse effects of hypercortisolemia on the progression of coronary artery disease, especially on the background of comorbid diabetes mellitus type 2 and anemia.**Ключові слова:** ішемічна хвороба серця, цукровий діабет типу 2, анемія, кортизол.*Буковинський медичний вісник*
2020. Т.24, № 3 (95), С. 68-72.**РОЛЬ ГІПЕРКОРТИЗОЛЕМІЇ В ПОЄДНАНОМУ ПЕРЕБІГУ ІШЕМІЧНОЇ ХВОРОБИ СЕРЦЯ, ЦУКРОВОГО ДІАБЕТУ ТИПУ 2 ТА АНЕМІЇ***Н.Д. Павлюкович, О.В. Павлюкович, В.О. Шупер, О.В. Залівська***Резюме****Мета роботи** – дослідження динаміки змін синтезу кортизолу у пацієнтів старших вікових груп з ішемічною хворобою серця (ІХС) з коморбідними цукровим діабетом типу 2 (ЦД) та анемічним синдромом (АС).**Матеріал і методи.** Рівень кортизолу в крові досліджували в 40 пацієнтів старшого віку з ІХС з коморбідними ЦД і АС різного

ступеня тяжкості. Контрольну групу склали 12 пацієнтів з ІХС без супутніх захворювань, які за статтю та віком достовірно не відрізнялися від пацієнтів дослідних груп. Також досліджені можливі ефекти телмісартану на ступінь хронічної гіпоксії.

Результати. У пацієнтів літнього та старечого віку з ІХС та коморбідним АС, як і у випадку ІХС та АС на тлі ЦД, спостерігається активація синтезу кортизолу, ймовірно, у відповідь на гіпоксію як фактор стресу при анемії. Ступінь вираженості виявлених змін різниться залежно від ступеня тяжкості супутньої анемії. Не спостерігалось нормалізації вмісту кортизолу в крові в жодній із дослідних груп, незалежно від призначеного лікування інгібіторами АПФ або телмісартаном.

Висновки. У пацієнтів з ішемічною хворобою серця, як і при коморбідному перебігу ішемічної хвороби серця та цукровим діабетом, має місце збільшення секреції кортизолу у відповідь на анемічну гіпоксію. Із прогресуванням ступеня тяжкості анемічного синдрому рівень кортизолу в крові поступово знижується. Зниження напруженості стрес-лімітувальних систем організму в результаті призначення телмісартану може сприяти усуненню несприятливих ефектів гіперкортизолемії на прогресування ішемічної хвороби серця, особливо на тлі супутніх цукрового діабету типу 2 та анемії.

Ключевые слова: ишемическая болезнь сердца, сахарный диабет типа 2, анемия, кортизол.

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РОЛЬ ГИПЕРКОРТИЗОЛЕМИИ В СОЧЕТАННОМ ТЕЧЕНИИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА, САХАРНОГО ДИАБЕТА ТИПА 2 И АНЕМИИ

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Резюме

Цель работы – исследование динамики изменений синтеза кортизола у пациентов старших возрастных групп с ишемической болезнью сердца (ИБС) с коморбидными сахарным диабетом типа 2 (СД) и анемическим синдромом (АС).

Материал и методы. Уровень кортизола в крови исследовали у 40 пациентов старшего возраста с ИБС с коморбидными СД и АС различных степеней тяжести. Контрольную группу составили 12 пациентов с ИБС без сопутствующих заболеваний, которые по полу и возрасту достоверно не отличались от пациентов исследуемых групп. Также были изучены возможные эффекты телмисартана на степень хронической гипоксии.

Результаты. У пациентов пожилого и старческого возраста с ишемической болезнью сердца и коморбидным АС, как и в случае ИБС и АС на фоне СД, наблюдается активация синтеза кортизола, вероятно, в ответ на гипоксию как фактор стресса при анемии. Степень выраженности выявленных изменений различается в зависимости от степени тяжести сопутствующей анемии. Не наблюдалось нормализации содержания кортизола в крови в одной из исследуемых групп независимо от назначенного лечения ингибиторами АПФ или

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телмисартаном.

Выводы. У пациентов с ишемической болезнью сердца, как и при коморбидном течении ишемической болезни сердца и сахарном диабете, имеет место увеличение секреции кортизола в ответ на анемическую гипоксию. По мере прогрессирования степени тяжести анемического синдрома уровень кортизола в крови постепенно снижается. Снижение напряженности стресс-лимитирующих систем организма в результате назначения телмисартана может способствовать устранению неблагоприятных эффектов гиперкортизолемии на прогрессирование ишемической болезни сердца, особенно на фоне сопутствующих сахарного диабета типа 2 и анемии.

Introduction. The human stress response has evolved to maintain homeostasis under conditions of real or perceived stress [1]. This objective is achieved through autoregulatory neural and hormonal systems in close association with central and peripheral clocks. The hypothalamic-pituitary-adrenal axis is a key regulatory pathway in the maintenance of these homeostatic processes. Cortisol, produced by the hypothalamus-pituitary-adrenal axis during stress response, is still not included in the routine evaluation of cardiovascular risk and requires additional and definitive validation [2].

In acute stress, hypersecretion of cortisol in the body is observed. There are many possible pathological reactions associated with this fact [3]: sympatho-adrenal activation with susceptibility to vasoconstriction, decreased heart rate variability, hyperaggregation of thrombocytes, increased heart rate, arterial hypertension, increased C-reactive protein and pro-inflammatory cytokines levels, interleukin-1 and interleukin-6 secretion. Increased levels of cortisol also contribute to the development and progression of heart failure and atherosclerotic processes [4, 5]. Through these mechanisms stress can provoke cardiovascular diseases.

The aim of the study - investigation of changes of the cortisol secretion in patients with coronary artery disease with comorbid diabetes mellitus type 2 and anemic syndrome in patients of older and senile age and determining possible interconnection between revealed changes and anemic hypoxia severity.

Material and methods. Due to the fact that synthesis of certain glucocorticoid in stress conditions is species-specific, and human beings are characterized by cortisol secretion, namely by the level of this hormone in the blood serum we have estimated glucocorticoid function of the adrenal cortex.

Blood cortisol level was measured in 40 old and senile CAD patients with comorbid DM and AS of different degrees of severity. Average age of the investigated patients was $67 \pm 4,5$ years. Control group consisted of 12 patients with CAD without comorbidities that were not significantly different by gender and age from patients of research groups. All patients were treated for their main and comorbid diseases (aspirin,

beta-blocker, statin, ACE inhibitor), additionally telmisartan was prescribed. Therefore, patients with CAD, DM and anemia additionally were randomized into groups depending on the prescribed treatment: A – 20 patients who received only basic therapy and B – 20 patients whom in the scheme of the basic treatment replacement of ACE inhibitor by angiotensin receptor blockers II telmisartan was performed, the last was prescribed in a dose 40 mg daily after meals. Duration of in-hospital treatment was 21-24 days, additionally telmisartan was prescribed for out-hospital treatment during 4-6 months.

Investigation of cortisol levels in blood plasma was performed by immunoassay analysis on the RT-2100C (Rayto Electronics Inc., China) immunoassay analyzer. A set of reagents Kortizol-IFA (OOO Hema-Medica, Russia) was used with range of normal values from 150 to 650 nmol/l.

Results. Cortisol content in blood serum of patients of the control group was $390,8 \pm 52,67$ nmol/l, which was within the physiological norm (Fig. 1). We did not detect significant changes in cortisol blood level due to comorbid course of CAD and DM: cortisol content in the blood serum was $476,7 \pm 39,11$ nmol/l ($p > 0,05$ compared with the control group), which also was within normal values. In patients with CAD and comorbid anemia of different degrees of severity cortisol content was 2,02 times higher ($p < 0,05$) and was $966,2 \pm 66,51$ nmol/l. In case of complication of CAD by DM and AS cortisol level in blood was slightly lower ($897,4 \pm 38,43$ nmol/l) and significantly different from the similar value in the control group ($p < 0,05$) and patients with CAD and DM without anemia ($p < 0,05$).

Thus, as in patients with CAD and comorbid AS, same as in case of CAD and AS on the background of DM, activation of the glucocorticoid function of the adrenal cortex and significant hypercortisolemia are observed, likely in response to hypoxia as a stress factor in anemia.

Taking into consideration higher incidence of mild anemia compared with moderate and severe degree among patients with CAD and DM type 2, it can be assumed that the effect and course of the disease affect

the degree of hypercortisolemia. This made us to compare the values of the cortisol content in serum in patients of the main groups depending on the severity of the comorbid AS.

As seen in Fig. 2, in patients with CAD and mild anemia compared with patients of the control group

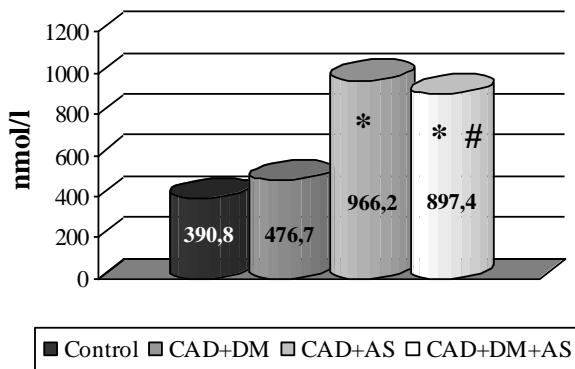


Fig. 1. Cortisol level in serum of patients with coronary artery disease, diabetes mellitus type 2 and anemic syndrome

Note: * – difference is valid against patients of control group ($p < 0,05$); # – difference is valid against patients with CAD and DM ($p < 0,05$)

significant increased of cortisol blood content was observed. Obviously, anemia aggravates hypoxia, which occurs in CAD patients due to decreased cardiac output and insufficient perfusion of organs and tissues, which results in compensatory activation of cortisol secretion. With progression of anemia severity we observed tendency to depletion of the glucocorticoid function of adrenal cortex with decreasing of the content of serum cortisol, which, however, was not statistically significant ($p > 0,05$). For CAD and anemia of moderate severity cortisol level was $883,2 \pm 87,78$, which was 10% less than in patients with anemia of mild degree.

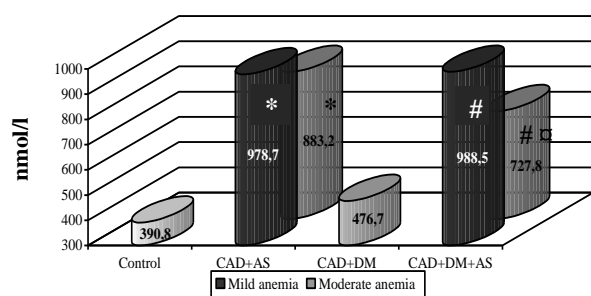


Fig. 2. Cortisol level in serum of patients with coronary artery disease and diabetes mellitus type 2 depending on the anemic syndrome severity

Note: * – difference is valid against patients of control group ($p < 0,05$); # – difference is valid against patients with CAD and DM ($p < 0,05$); □ – difference is valid against patients with CAD, DM and mild anemia ($p < 0,05$)

Similar tendency of the changes of cortisol blood level due to the degree of anemic hypoxia was observed

in case of comorbid course of CAD, DM and anemia. In patients with CAD and DM comorbid to mild anemia there was statistically significant increase of the cortisol content of blood serum in 2,07 times compared with patients with CAD and DM ($p < 0,05$), which may be considered as activation of the stress-limiting possibilities of the organism in response to hypoxia. Along with progression of the comorbid anemia degree of severity, there was a progressive depletion of the glucocorticoid function of adrenal glands, accompanied by a statistically significant decrease in cortisol blood content by 26% compared with the same figure in patients with CAD, DM and mild AS ($p < 0,05$), the values of which, however, did not reach the corresponding value in the group of patients with CAD and DM.

As a result of the conducted treatment, patients in both experimental groups were characterized by a certain dynamics of changes in the cortisol blood level, which was manifested by a marked tendency to reduction of the hypercortisolemia in the blood serum of patients with CAD, DM type 2 and comorbid anemia (Fig. 3). The degree of severity of the detected changes was different depending on the type of treatment.

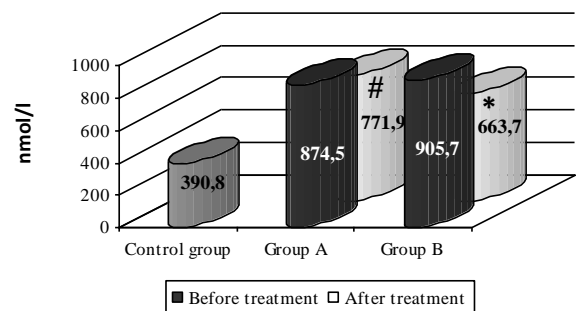


Fig. 3. Cortisol level in serum of patients with coronary artery disease, diabetes mellitus type 2 and anemia depending on the prescribed treatment

Note: * – difference is valid against patients before and after treatment ($p < 0,05$); # – difference is valid against patients of control group ($p < 0,05$)

In patients of group A, treated by standard scheme of treatment (aspirin, beta-blocker, statin, ACE inhibitor), cortisolemia decreased by 12% compared with its corresponding values before treatment ($771,9 \pm 93,10$ and $874,5 \pm 41,12$ nmol/l, respectively), which, however, was not statistically significant ($p > 0,05$) and 1,97 times higher than that in the control group ($p < 0,05$). The average level of cortisol in patients of group B (where ACE inhibitor was replaced by telmisartan because of low adherence of the patients to prolonged treatment by ACE inhibitor) was $663,7 \pm 96,69$ nmol/l, statistically significantly differing by 27% for its corresponding value before treatment ($p < 0,05$). There was no normalization of cortisol content in blood in any of the major experimental groups.

Conclusions. Thus, in patients with CAD and anemia, same as in case of a comorbid course of CAD, AS and DM, an increase of cortisol secretion in response

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to anemic hypoxia was observed. As the degree of severity of the comorbid AS progressed, gradual significant decreasing of hypercortisolemia level was detected. Therefore chronic hypoxia in patients with comorbid course of CAD, DM and anemia, particularly of mild degree of severity, may contribute to constant hypercortisolemia, progression of CAD and increasing of general cardiovascular risk. Progression of comorbid anemia severity in such patients may partially play a protective role as it is characterized by decreasing of hypercortisolemia degree. Reducing the intensity of stress-limiting systems in the organism may help to eliminate the adverse effects of hypercortisolemia on the progression of coronary artery disease, especially on the background of comorbid diabetes mellitus type 2 and anemia. Prescription of telmisartan in such patients may have some benefits over ACE inhibitors taking into consideration positive its effects on the decreasing of blood cortisol levels.

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