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ERYTHROPOIETIN SYNTHESIS IN PATIENTS WITH CHRONIC HEART FAILURE DEPENDING ON COMORBID PATHOLOGY

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Summary

Introduction. Decreased production of erythropoietin by the kidneys plays crucial role in the development of anemia in patients with chronic heart failure, especially on the background of comorbid diabetes mellitus type 2. In diabetic patients due to early damage of the kidney vessels and following erythropoietin deficiency anemia develops much earlier than clinically significant decrease of glomerular filtration rate.

The aim of the study was to find out possible dependence of changes in the erythropoietin-synthesizing function of the kidneys on the degree of severity of anemic hypoxia in elderly and senile patients with chronic heart failure, including those with comorbid type 2 diabetes mellitus.

Materials and methods. 120 patients with chronic heart failure of ischemic origin, type 2 diabetes mellitus and mild and moderate anemia were examined. Control group comprised 12 people with chronic heart failure without comorbid pathology. The examined groups were comparable in terms of gender and age, differing in the presence of comorbid diabetes mellitus and degree of severity of anemic syndrome. The level of erythropoietin in blood serum was determined by standard enzyme-linked immunosorbent assay.

Results. Type 2 diabetes mellitus in patients with chronic heart failure results in a significant decrease in erythropoietin production by 25 % compared to the control group ($p < 0,05$). Comorbid to heart failure anemia leads to an increase in the level of erythropoietin by 74,4 % ($p < 0,05$), and in the case of chronic heart failure and type 2 diabetes mellitus on the background of concomitant anemia – only by 39,5 % ($p < 0,05$). As the severity of anemia in patients with chronic heart failure without diabetes progresses, the severity of the compensatory response of the kidneys to chronic anemic hypoxia is significantly higher than in patients with heart failure and comorbid type 2 diabetes.

Conclusions. Diabetic nephropathy in patients with chronic heart failure and comorbid anemia leads to a significant deterioration of the erythropoietin-synthesizing function of the kidneys, complicating the course of both main and comorbid diseases.

Key words: chronic heart failure, diabetes mellitus type 2, anemia, hypoxia, erythropoietin

INTRODUCTION

Nowadays comorbidity tends to be considered the rule rather than the exception, so increasing awareness and improving guidance for patients with comorbid conditions is crucial in order to prevent adverse health outcomes, increase efficiency, and reduce costs [1]. One of the first steps in this process is to assess the prevalence of comorbidity in CVD and to provide a context for future research.

Chronic heart failure (CHF), renal dysfunction, anemia, and iron deficiency affect each other and form a vicious cycle, a condition referred to as cardiorenal anemia iron deficiency syndrome. The presence of diabetes mellitus (DM) further accelerates this vicious cycle [2]. Diabetes comorbidity is a poor prognostic predictor in patients with heart failure. Diabetes is often complicated by renal dysfunction, which further increases the risk of developing heart failure. On the other hand,

heart failure in diabetes adversely affects the kidneys. The function of the kidney is tightly linked to the function of the heart. Dysfunction / disease of the kidney may initiate, accentuate, or precipitate of the cardiac dysfunction / disease and vice versa, contributing to a negative spiral. Further, the reciprocal association between the heart and the kidney may occur on top of other entities, usually diabetes, hypertension, and atherosclerosis, simultaneously affecting the two organs [3].

Despite the fact that renal anemia can be due to different reasons (iron deficiency, latent blood loss, chronic hypoxia, etc.) [4, 5], according to the literature data, the main role in its development belongs to the lack of erythropoietin (EPO), a glycoprotein which is synthesized by peritubular fibroblasts of the cortical layer of the kidneys and physiologically regulates the process of erythrocyte maturation [6].

THE AIM OF THE RESEARCH

The analysis of the peculiarities of erythropoietin secretion by the kidneys in patients with chronic heart failure on the background of comorbid diabetes mellitus and anemic syndrome.

MATERIALS AND METHODS

Research included 120 elderly and senile male patients with comorbid course of CHF due to coronary artery disease, DM type 2 and anemia of different degrees of severity who were admitted to the cardiological department due to CHF exacerbation. All enrolled patients gave consent for the investigation. According to the comorbid pathology patients were randomized to the following groups:

I – patients with CHF and comorbid DM type 2 (n=12);

II – patients with CHF and anemia of different degrees of severity (n=32)

III – patients with CHF, DM type 2 and anemia of different degrees of severity (n=76)

Control group for comparative studies consisted of 12 patients with CHF without comorbid pathology, whose age statistically did not significantly differ from the average age of patients in the research groups.

CHF was diagnosed according to 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [7] and corresponded stage C NYHA II-III; it was due to chronic forms of coronary artery disease (stable exertional angina, post myocardial infarction cardiosclerosis). Anemia was considered as hemoglobin level below 130 g/L (WHO's Recommendations, 2003). DM type 2 was diagnosed by endocrinologist according to consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [8]. The average duration of DM was $3,2 \pm 1,11$ years. All examined patients were diagnosed with mild and moderate degree of diabetes severity. Exclusion criteria from the study were any comorbid diseases during the exacerbation period, oncological pathology, known bleeding of any localization, previously diagnosed kidney diseases, any surgical interventions in the anamnesis.

Patients of II and III groups were additionally randomized based on the degree of anemia severity (fig. 1).

Erythropoietin-synthesizing function of the kidneys was assessed by the level of erythropoietin in the blood serum. EPO was detected by enzyme-linked immunosorbent assay using a set of erythropoietin reagents. The range of values of 4,3-32,9 mIU/mL for serum EPO was considered normal values.

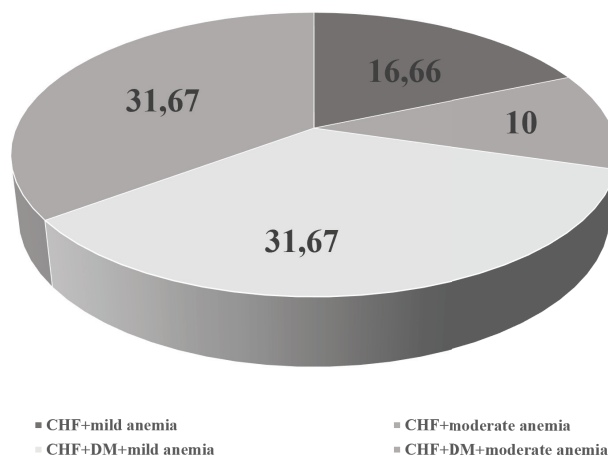


Fig. 1. Distribution of patients of research groups based on degree of anemia severity

RESULTS AND DISCUSSION

Analysis of the obtained results are given on the figure 2.

Average value of the EPO level in patients of the control group coincides with the lower limit of the normal range of values. In patients with comorbid course of CHF and DM type 2, decrease in serum EPO by 25 % against control group ($p < 0,05$) was detected, which, in our opinion, may be conditioned by violation of the

physiological secretion of erythropoietin due to damage of the tubulointerstitial tissue of the kidneys as a result of chronic hyperglycemia and development of diabetic nephropathy. In patients with CHF and comorbid anemia, on the contrary, statistically significant increase in EPO content in blood serum was observed in comparison with control group ($7,5 \pm 0,16$ vs. $4,3 \pm 0,14$ mO/ml, $p < 0,05$), which could be understood as existing mechanism between the severity of hypoxia and degree of erythropoietin synthesizing function of the kidneys.

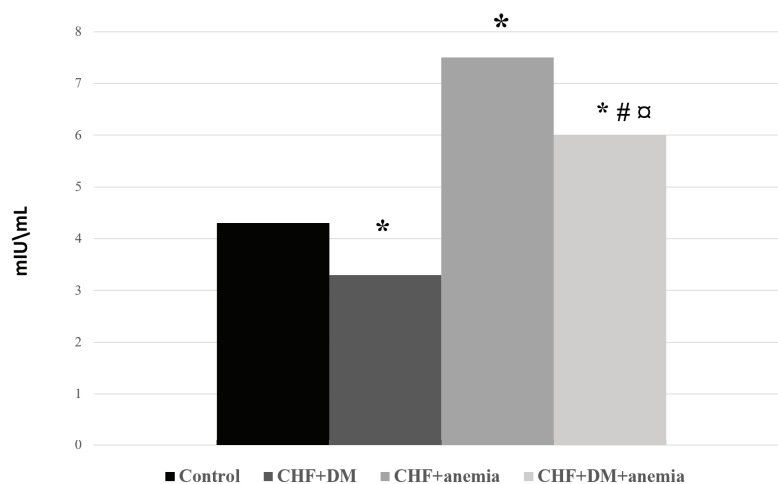


Fig. 2. Erythropoietin content in blood serum of patients with chronic heart failure, diabetes mellitus type 2 and anemia ($M \pm SEM$)

Note: * – difference is significant compared to patients of control group ($p < 0,05$); # – difference is significant compared to patients with chronic heart failure and diabetes mellitus ($p < 0,05$); □ – difference is significant compared to patients with chronic heart failure and anemia ($p < 0,05$)

The following interesting pattern was observed in case of comorbid course of CHF, DM type 2 and anemia. Decrease of hemoglobin and existing hypoxia in patients with CHF and DM results in a probable increase in serum EPO almost twice, compared with patients with CHF and DM without anemia ($p < 0,05$), which may indicate a relatively preserved erythropoietin-synthesizing function of the kidneys even in case of diabetic nephropathy. However, presence of statistically significant difference between EPO levels in patients with CHF and anemia in comparison with patients with CHF, anemia and DM type 2 in the direction of its decreasing ($7,5 \pm 0,16$ vs. $6,0 \pm 0,23$ mO /ml, $p < 0,05$) proves in favor of the fact that along with stimulating effect of hypoxia on kidney function in this category of patients, it is important to prevent the progression of their diabetic lesions in order to preserve the functional ability of the kidneys to adequately respond to this stress factor.

Regarding the fact that in all examined patients with comorbid anemia compared to those with normal hemoglobin level relatively higher levels of EPO in the blood were detected, we analyzed possible connection

between serum erythropoietin level and severity of the comorbid anemic syndrome.

We found out that along with blood hemoglobin level decreasing in patients with CHF, there is a statistically significant increase of the content of EPO in blood serum (Fig. 3) by 28 % with comorbid mild anemia ($p < 0,05$) and twice more in patients with comorbid anemia of moderate severity ($p < 0,05$). Serum EPO levels differed also in patients with CHF and moderate anemia compared to patients with CHF and mild anemia ($p < 0,05$). Similar tendency was observed in case of comorbid course of CHF and DM type 2 diabetes and anemia: the relationship between level of hemoglobin and erythropoietin had a statistically significant inverse character ($p < 0,05$).

However, it is worth noting that as the severity of anemia in patients with CHF without DM increases, intensity of the compensatory response of the kidneys to chronic hypoxia is significantly higher than in patients with CHF and comorbid DM type 2. In patients with CHF complicated by moderate anemia, level of serum EPO increased almost twice compared to such patients with comorbid mild anemia, while in case of comorbid course of CHF, DM and anemia it increased by only 17,8 %.

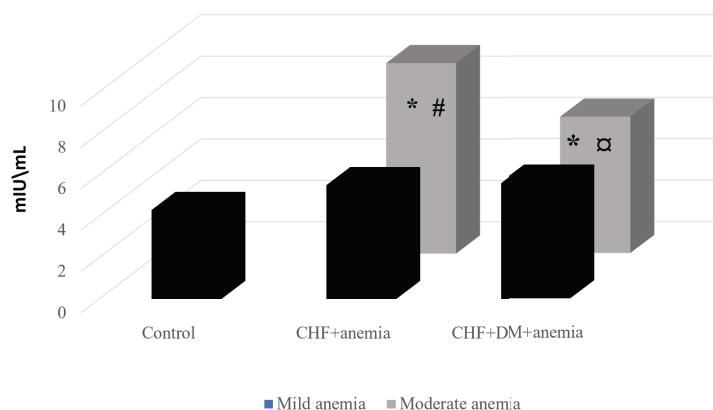


Fig. 3. Changes of erythropoietin-synthesizing function of kidneys in patients with chronic heart failure and diabetes mellitus depending on the severity of comorbid anemia

Note: * – difference is significant compared to patients of the control group ($p < 0,05$); # – difference is significant compared to patients with chronic heart failure and mild anemia ($p < 0,05$); □ – difference is significant compared to patients with chronic heart failure, diabetes mellitus type 2 and mild anemia ($p < 0,05$)

CONCLUSIONS

In elderly and senile patients with chronic heart failure without comorbid diabetes mellitus type 2 and anemia erythropoietin-synthesizing function of the kidneys is preserved, although absolute values of EPO content in blood serum of these patients are close to the lower limit of the range of normal values. In case of complication of CHF by anemia, there is significant increase of the serum EPO level, the degree of which depends on the severity of the comorbid anemia and serves as a compensatory mechanism of the organism

under conditions of prolonged exposure to chronic hypoxia. Type 2 diabetes mellitus, causing signs of diabetic nephropathy in patients, leads to a significant decrease in the production of erythropoietin by the kidneys in patients with chronic heart failure, and in the case of a comorbid course of chronic heart failure, diabetes mellitus type 2 and anemia, it strongly reduces the compensatory capabilities of the latter.

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Резюме

СИНТЕЗ ЕРИТРОПОЕТИНУ У ХВОРИХ НА ХРОНІЧНУ СЕРЦЕВУ НЕДОСТАТНІСТЬ ЗАЛЕЖНО ВІД КОМОРБІДНОЇ ПАТОЛОГІЇ

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Вступ. Зниження продукції нирками еритропоетину має важливе значення у розвитку анемії у хворих на хронічну серцеву недостатність, особливо на фоні супутнього цукрового діабету 2-го типу. При цукровому діабеті внаслідок раннього ураження судин нирок та дефіциту еритропоетину, анемія розвивається значно раніше, ніж клінічно значиме зниження швидкості клубочкової фільтрації.

Метою дослідження стало вивчення імовірної залежності змін еритропоетинсинтезуючої функції нирок від ступеня тяжкості анемічної гіпоксії у хворих на хронічну серцеву недостатність літнього та старечого віку, у тому числі на тлі коморбідного цукрового діабету 2-го типу.

Матеріали та методи дослідження. Обстежено 120 хворих на хронічну серцеву недостатність ішемічного генезу, цукровий діабет 2-го типу та анемію легкого та середнього ступеня тяжкості. Контрольну групу склали 12 осіб із серцевою недостатністю без супутньої патології. Групи обстеження були співставними за статтю та віком, відрізняючись наявністю супутнього цукрового діабету та ступенем тяжкості анемічного синдрому. Рівень еритропоетину сироватки крові визначали за стандартною імуноферментною методикою.

Результати дослідження. Цукровий діабет 2-го типу у хворих на хронічну серцеву недостатність супроводжується суттєвим зниженням продукції еритропоетину на 25 % у порівнянні з контрольною групою ($p < 0,05$). Супутня анемія призводить до підвищення рівня еритропоетину на 74,4 % ($p < 0,05$), а у випадку перебігу хронічної серцевої недостатності та цукрового діабету 2-го типу на тлі супутньої анемії – лише на 39,5 % ($p < 0,05$). У міру прогресування ступеня тяжкості анемії при серцевій недостатності без цукрового діабету ступінь вираженості компенсаторної відповіді нирок на хронічну анемічну гіпоксію є значно вищою, ніж у хворих на серцеву недостатність та супутній цукровий діабет 2-го типу.

Висновки. Діабетична нефропатія у хворих на хронічну серцеву недостатність та супутню анемію призводить до суттєвого погіршення еритропоетинсинтезувальної функції нирок, ускладнюючи перебіг як основного, так і супутніх захворювань.

Ключові слова: хронічна серцева недостатність, цукровий діабет 2-го типу, анемія, гіпоксія, еритропоетин