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ANEMIA OF CHRONIC DISEASE (ACD) IN HEART AND RESPIRATORY FAILURE: A COMPARATIVE ANALYSIS

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Abstract. Anaemia of chronic disease (ACD) is second after iron deficiency anaemia. It masks the clinical presentations of the main disease and worsens the prognosis and effectiveness of treatment, but its prevalence, impact and mechanisms have not been established yet.
Aim: to study the frequency, clinical impact and role of inflammation in ACD in patients with chronic heart (CHF) and chronic respiratory (CRF) failures.
Methods: we did a literature review using thePubmed database and national sources and analysed medical records of 500 patients with coronary artery disease, stable stenocardia, CHF and 470 patients with chronic obstructive pulmonary disease, CRF. The results were statistically checked using the Student's criteria and Kaplan-Mayer method with Cox and Gehan-Wilcoxon criteria. Results were considered significant if $p < 0.05$.
Results: Anaemia is diagnosed equally and frequently in heart or respiratory failure (32%)and is twice as common among men. The anaemia was generally mild in both organs failures, but CRF was accompanied by a higher rate of moderate and severe forms. The normochromic normocytic character of ACD was predominate in both types of failures, but the patients with CRF had a higher incidence of hyperchromia and less often had microcytosis. Anaemia of chronic disease has multifactorial pathogenesis: inflammation, impaired iron metabolism, renal dysfunction, malabsorption, hemodilution, and medications. Anaemia affects the clinical manifestations of main pathology, its course and prognosis; it was an independent predictor of shortersurvival range in CRF and CHF at 36 months (58.9% vs 82.3%, Cox F–test p=0.01; test Gehan-Wilcoxon p=0.053).

Key words: anaemia of chronic disease, chronic heart failure, chronic respiratory failure.

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Introduction

Anaemia of chronic disease (ACD) is one of the least understood comorbid syndromes ininternal medicine [1]. The leading mechanism of ACD is inflammation, which is confirmed by an increase in almost all markers of inflammation: cytokines (interleukins IL–6, –10, –8, -1β, -1α) and adipocytokines (leptin), tumour necrosis factor alpha (TNFα), gamma–interferon, C-reactive protein (SRP), fibrinogen, surfactant protein D, serum amyloid A, migration factors and the activation of cellular elements [2, 3]. However,ACD is also foundin patients with diseases in which the inflammatory mechanism is not crucial [1,4–6]: chronic kidney disease, chronic heart and respiratory failures, pulmonary hypertension, obesity, strokes, celiac disease, etc. ACD developsviaseveral different mechanisms, among them the most important are the influence of an excess of proinflammatory cytokines and endotoxic substances and disorders of iron metabolism, as well as renal dysfunction, malabsorption, hemodilution, and using the medications (aspirin, angiotensin-converting enzyme) [1, 7, 8]. Researchers pay a lot of attention to ACD in patients with heart and respiratory failures because they determine the quality and duration of life and clinical symptoms, and theycontribute to determining the long-term prognosis and life expectancy [6,7]. However, the pathogenetic mechanisms of the development of heart and respiratory failures are different, so there is a question of the peculiarities of ACD under those conditions, which determines the feasibility and relevance of further research in this area.

Aim

Aim to study the frequency, impact and mechanisms of ACD in the patients with chronic heart (CHF) and chronic respiratory failure (CRF).

Material and methods

Retrospective analysis of medical records of 500 patients (men 352, women 144) with CHF (coronary artery dise-

ase (CAD), stable angina) and 470 people (men 246, women 224) with CRF (chronic obstructive pulmonary disease, COPD) was done. Patients were examined and treated in a hospital according to the international guidelines, in compliance with the Declaration of the World Medical Association on the Ethical Principles of Conducting Scientific Medical Research with Human Participation. A level of erythropoietin in the blood was determined by enzyme-linked immunosorbent assay with Erythropoietin-ELISA-BEST reagent (Vector Best, Russia). The criteria of ACD were:

1. Normochromic (haemoglobin content in the erythrocyte MCHC 32-36 g/l or less often MCHC 26-31.5 g/l) normocytic (or microcytic, MCV<80 fl) character.
2. Decreased concentration of serum iron (< 12.5 mkmol/l).
3. Reduced transferrin saturation of iron.
4. Changes in the ferritin concentration (more frequent increase, less frequently the norm or decrease).
5. The normal number of transferrin receptors (sTFR), but their ratio to the log of ferritin is <1.0.
6. The content of iron in bone marrow macrophages is slightly increased.
7. Bone marrow: hypoproliferation with different availability of iron for haemoglobin synthesis [8–12]. There are a lot of discussions about the haemoglobin (GL) level for patients with CHF and CRF, which have been suggested to be greater than healthy people and equal for women and men [7, 12].

The statistical processing was performed using the Statistica for Windows 6.0 software package (Statsoft, USA). We used parametric statistical methods after a normality check. The results were considered significant if p<0.05, using the Student's t–test. Survival range was checked by Kaplan–Meier test, and the difference between groups was determined by Cox and Gehan–Wilcoxon criteria.

Results and discussion

The academicdata on the epidemiology of ACD are few and contradictory, and the disease's prevalence is still completely unknown: the frequency of ACD ranges from 6.6% to 50% [5–7, 9, 13], or even up to 80% [14]. The researchers foundthat the prevalence of ACD in CRF is similar to that of CHF [6, 7].

According to our own data, among 500 patients with CHF anaemia was detected in 158/31.6 ± 2.1% of patients (70.0% were men and 30.0% women), and among 470 patients with CRF it was found in 150/31.9 ± 3.8% of persons (61.3% of men and 38.07% of women) [15–17]. That is, the prevalence of anaemia in CHF and CRF is the same in almost a third of patients, almost twice as often inmen.

Mild forms of ACD were noticedin both types of functional organ failure, but CRF was accompanied by more severe forms of anaemia. Thus, patients with CHF were most often diagnosed with mild anaemic syndrome (93.4 ± 2.0%), rarely – medium severity (5.0 ± 1.7%) and severe (1.6 ± 1.0%). The milder form was diagnosed more frequently in the patients with CRF too, the frequency of which was, however, less (72.3 ± 3.6%, $p < 0.05$), but moderate severity (20.3 ± 3.3%, $p < 0.05$) and severe (6.8 ± 2.0% $p < 0.05$) forms were diagnosed more often than in CHF. Moreover, extremely severe ACD, although rare, was only found in the patients with CRF (0.7 ± 0.7%). Thus, in the face of both organ's failures anaemia was significantly more often mild than moderate orsevere, but CRF was accompanied by increasing moderate and severe forms.

According to the literature, ACD is usually normocytic normochromic but may be microcytic hypochromic also [11, 12]. It was diagnosed normocytic character of anaemia according to MCV and normochromic according to MCHC in the most patients with CHF (71.6 ± 2.8% and 83.1 ± 2.3%); microcytosis and erythrocyte hypochromia were detected in 21.0 ± 2.5% and 15.8 ± 2.3%, macrocytosis and hyperchromia– in 7.4 ± 1.6% and 1.1 ± 0.65%. The patients with CRF in comparison with CHF have significantly more often normocytic character of anaemia (96.0 ± 1.1%, $p < 0.05$), equally often normochromic (76.5 ± 3.5%); significantly less often microcytic (2.0 ± 1.1%, $p < 0.05$) and equally often hypochromic (14.7 ± 2.9%); but the macrocytic character was less common with more frequent hyperchromia (2.0 ± 1.8%, 8.8 ± 2.3%). Therefore, in both types of failure the normochromic normocytic character of anaemic syndrome was equally prevalent, but a lower incidence of microcytosis but higher hyperchromia were observed in patients with CRF. In addition, ACD was often accompanied by a mismatch of red blood cell size and saturation of haemoglobin (HG) level, which was observed in 23.0 ± 3.3% of patients with CHF and significantly more frequently in CRF (39.0 ± 4.0%; $p < 0.05$), which may also indicate different mechanisms of their pathogenesis.

According to our own investigations, the severity of systemic inflammation in patients with CHF and anaemia was higher according erythrocyte sedimentation rate (ESR) (13.7 ± 0.7 vs 8.0 ± 0.4 mm/h, $p < 0.05$) and the CRP level, which was 1.5 times higher than the norm. The similar manifestations were observed in patients with CRF and anaemia, when not only ESR was significantly higher (19.31 ± 1.2 vs 14.19 ± 0.62 mm/h, $p < 0.05$), but also the content of bands (5.58 ± 0.40% vs 4.42 ± 0.20%, $p < 0.05$) and segmented neutrophils (68.33 ± 0.98% vs 63.78 ± 0.73%,

$p < 0.05$) and serum markers exceeded in 1.25–1.5 times the values of individuals without anaemic syndrome.

The activation of systemic inflammation begins to affect iron metabolism through conventional inflammation (IL, interferon, TNF) and iron metabolism specific (hepcidin, ferritin) markers [2, 12, 18]. The iron metabolism impairment with decreased iron in the blood with normal or elevated content in the reticuloendothelial system is the second main mechanism of ACD development. According to our data, in patients with CHF and anaemia the level of iron was more often slightly reduced (65.7%, by 8% from normal range) or normal (34.3%). That was accompanied by different values of blood erythropoietin levels: elevated (53.8%), normal (37.5%) or even decreased (8.7%).

Anaemic syndrome influences the manifestations, course and prognosis of the main pathology: ACD in patients with both CHF and CRF is described as an independent factor of more frequent hospitalizations, mortality [3,10,14–16,19,20] and poor mental health [3, 6, 7]. In our patients the ACD affected the clinical manifestations of CHF and its severity significantly: under its conditions the I-II functional classes (FC) by NYHA classification were registered less frequently (11.2% vs 20.5%, $p < 0.05$), while the III–IV FC was significantly more frequent (27.5% vs 10.8%, $p < 0.05$); the frequency of systolic dysfunction was significantly greater ($55.8 \pm 3.9\%$ vs $39.2 \pm 3.0\%$, $p < 0.05$); the cardiac arrhythmias were diagnosed 1.5 times more often (atrial fibrillation in 38.0% vs 22.8%, $p < 0.05$). A similar clinical effect was found in individuals with CRF with ACD. The IV degree of CRF severity ($9.33 \pm 2.37\%$ vs $3.44 \pm 1.02\%$, $p < 0.05$) and group D of COPD ($70.00 \pm 3.74\%$ vs $14.06 \pm 5.18\%$, $p < 0.05$) were noticed more often. Moreover, fewer ranges of oxygen saturation ($92.69 \pm 0.80\%$ vs $96.00 \pm 0.41\%$, $p < 0.05$), lung vital capacity ($63.66 \pm 1.62\%$ and $69.67 \pm 0.99\%$, $p < 0.05$) and its forced value ($67.38 \pm 1.09\%$ and $70.95 \pm 0.99\%$, $p < 0.05$) were noticed during pulmonary lung function investigation.

ACD itself proved to be a factor of the negativeprognosis: the cumulative part of the survival without events during 36 months in the patients with CHF and ACD was 58.9% and without it 82.3% (Cox F–test p=0.01; Gehan–Wilcoxon test p=0.053) (Fig.1). The numbers were even lower with severe anaemia: after 17 months, the cumulative survival rate was 16.7% vs 38.8% among people with mild ACD (Cox F–test p=0.037). Similarly, according to Menou A. et al. (2016), 64% of the patients with CRF with ACD had three–year survival and 93% without anaemia [2].

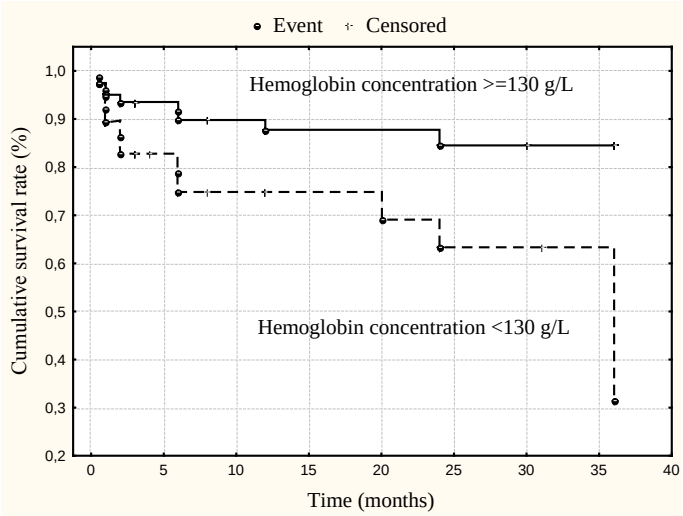

Figure 1: The curves of survival rate during 3 years in patients with chronic heart failure depending on the presence of anaemia of chronic disease.

Conclusions

Anaemia is diagnosed equally and as frequently in heart or respiratory failure (32%), twice as common inmen. The anaemia was generally mild in both organs failures, but CRF was accompanied by a higher rate of moderate and severe forms. The normochromic normocytic character of ACD was predominant in both types of failures, but the patients with CRF had higher incidence of hyperchromia and less often microcytosis. Anaemia of chronic disease has multifactorial pathogenesis: inflammation, impaired iron metabolism, renal dysfunction, malabsorption, hemodilution, and medications. Anaemia affects the clinical manifestations of main pathology, its course and prognosis; it was an independent predictor of worse survival periodin CRF and CHF during 36 months (58.9% vs 82.3%, Cox F–test p=0.01; test Gehan–Wilcoxon p=0.053).

Conflicts of Interest: the authors have no conflict of interest to declare.

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