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Blood Levels Dynamics of Aldosterone, Marker of Heart Failure NT-Probnp, a Proinflammatory Cytokine Tnfα, and Apoptosis Inducer FAS-Ligand Under the Influence of Enalapril with Candesartan in Patients with Decompensated Chronic Pulmonary Heart Disease

Vitaliy Seredyuk*[1]

1. Department of Internal Medicine no. 2, Ivano-Frankivsk, National Medical University, Ivano-Frankivsk, Ukraine
[E-mail: vseredyuk@inbox.ru, Tel. +380992339110]

The aim of our research was to investigate the effects of prolonged use of angiotensin converting enzyme (ACE) inhibitor enalapril and an angiotensin II receptor blocker (ARB) candesartan on the blood levels of aldosterone, N-terminal fragment of brain natriuretic peptide (NT-proBNP), tumor necrotic factor-α (TNF-α) and apoptosis inducer Fas-Ligand (FasL) in patients with decompensated chronic pulmonary heart disease (CPHD). 74 patients (11 women and 63 men) with decompensated CPHD with heart failure (HF) NYHA Class III were examined. Their average age was (62,8 ± 3,7) years. The patients were randomized into two clinical groups: the first (main) group consisted of 39 patients which additionally received the ARB candesartan (candesartan, "Ranbaxy", India-USA-Canada) and the second (control) group consisted of 35 patients which received only a basic therapy and ACE inhibitor enalapril. An increase in blood levels of aldosterone, marker of HF NT-proBNP, a proinflammatory cytokine TNF-α, and apoptosis inducer Fas-Ligand is marked in patients with decompensated CPHD with HF NYHA Class III, in comparison with healthy individuals. The combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan within 6 months promotes blood levels reduction of aldosterone, NT-proBNP, TNF-α, and FasL, that leads to the delay of HF progression in patients with decompensated CPHD

Keyword: Aldosterone, Marker of Heart Failure NT-proBNP, Proinflammatory Cytokine TNFα, Apoptosis Inducer Fas-Ligand, Enalapril, Candesartan, Chronic Pulmonary Heart Disease

1. Introduction

An activation of the renin-angiotensin-aldosterone system (RAAS) that was observed in case of chronic pulmonary heart disease (CPHD) with heart failure (HF) is accompanied by increased levels of mineralocorticoid aldosterone. The latter not only causes the retention of sodium and water and increases the excretion of potassium and magnesium, but also stimulates the development of fibrotic processes that contribute to the deterioration of systolic and diastolic functions of the right ventricle and to its remodeling[1,4]. A therapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) leads to a

decrease of aldosterone level and to leveling of its systemic neurohumoral effects[9, 10].

The evaluation of brain natriuretic peptide in blood is used with the goal to initially diagnose HF and to evaluate prognosis [20] under Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) of the European Society of Cardiology[12] and the Guidelines for the diagnosis and treatment of chronic heart failure (2012) of the Ukrainian Association of Cardiology and the Ukrainian Association of Heart Failure specialists[6]. An increase in concentration of brain natriuretic peptide and its inactive fragment - N-terminal fragment of brain natriuretic peptide (NT-proBNP) is an independent and a very important predictor of an unfavorable outcome in patients with heart failure of any etiology [7, 16].

In case of right ventricle HF an increase of NT-proBNP level in blood in consecutive measurements reflects the progression of right ventricular dilation (RV) and the deterioration of its systolic dysfunction[3, 17]. This allows the use of NT-proBNP to verify the diagnosis and evaluate treatment effectiveness of patients with right ventricular heart failure.

Some studies have shown that activation of cytokines with excessive expression of tumor necrotic factor-α (TNF-α) in chronic obstructive pulmonary disease (COPD)[2, 13] leads to damage of cardiomyocytes, cardiac remodeling and progression of heart failure[5, 18].

In recent years, appeared a small number of ambiguous reports that unfavorable prognosis of CPHD in case of COPD, on the one hand, is associated with activation of apoptosis of alveolar cells[8], which contributes to the progression of pulmonary hypertension[19] and, on the other hand, apoptosis of cardiomyocytes due to hypoxia[10], the marker of which is Fas-Ligand inducer[15]. These mechanisms lead to right ventricle remodeling and progression of heart failure in these patients[4].

In connection with the above mentioned, it is reasonable to study the influence of ACE inhibitor enalapril and the ARB candesartan on neurohumoral mechanisms of the development and progression of heart failure in patients with CPHD.

1.1 The Aim of Research

To study the influence of prolonged use of ACE inhibitor enalapril and the ARB candesartan on the level of aldosterone in blood, N-terminal fragment of brain natriuretic peptide, tumor necrotic factor-α and apoptosis inducer Fas-Ligand in patients with decompensated CPHD with HF NYHA Class III.

2. Materials and Methods

The study involved 74 patients (11 – women, 63 – men) with decompensated CPHD. Their average age was (62,8 ± 3,7) years.

Diagnosis CPHD due to COPD was made according to the recommendations of the International consensus "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease" (Updated 2013)[14].

Heart failure NYHA Class III was verified in all patients with decompensated CPHD under Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) of the European Society of Cardiology[12], and the Guidelines for the diagnosis and treatment of chronic heart failure (2012) of the Ukrainian Association of Cardiology, and the Ukrainian Association of Heart Failure specialists[6].

All patients received a basic CPHD therapy in accordance with the recommendations of the International Consensus "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease" (Updated 2013)[14], and a standard HF therapy under Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) of the European Society of Cardiology[12], and the Guidelines for the diagnosis and treatment of chronic heart failure (2012) of the Ukrainian Association of Cardiology, and the Ukrainian Association of Heart Failure specialists[6], which included ACE inhibitor enalapril (Enap, "KRKA", Slovenia) with the help of the titration method from 2,5 mg / day to a maximum tolerated dose. The patients have been divided

into two clinical groups: I (main) involved 39 patients who additionally received the angiotensin II receptor blocker candesartan (candesartan, "Ranbaxy", India-USA-Canada) with the use of the titration method from 4 mg / day to a maximum tolerated dose, and II (control) group that involved 35 patients who received only a basic therapy and enalapril. The dose of enalapril in the control group represented an average of (18, 5 ± 6,3) mg / day, in the main - (10,8 ± 4,1) mg / day and candesartan in the main group - (15,7 ± 5, 4) mg / day.

Determination of aldosterone level in blood ("DSL", USA), N-terminal fragment of brain natriuretic peptide NT-proBNP ("Peninsula", USA), a proinflammatory cytokine TNF-α ("Diaclone", USA) and apoptosis inducer Fas-Ligand ("Diaclone ", USA) was performed using an immunoenzyme method at the beginning of the research and after 6 months of the treatment. The indices of 27 healthy individuals, at (28, 4 ± 2,9) years of age served as criterion standard.

A statistical processing of the results was performed with the help of a personal computer and software packages Statistica v 8.0 ("Stat Soft", USA) and Clin Tools v4.1 ("Psytek Ltd", Australia).

We calculated the following indices: the arithmetic mean- M, the standard deviation from the arithmetic mean – m; t – Student's test for dependent and independent variables, the reliability coefficient – p (the difference was considered credible at $p < 0.05$) ; the Pearson criterion ($\chi 2$), Fisher's exact test (p, two-tailed).

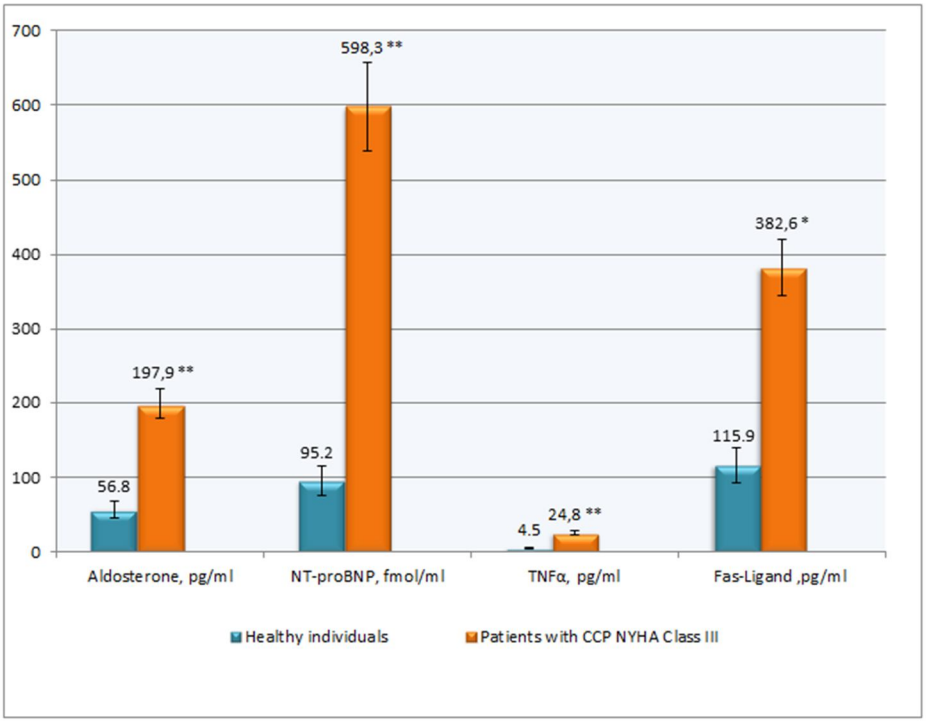

Figure 1: Blood levels of aldosterone, marker of heart failure NT-Probnp, a Proinflammatory cytokine TNFα, and apoptosis inducer Fas-Ligand in patients with decompensated CPHD with HF NYHA Class III in comparison with healthy individuals.

Note: The accuracy of difference in comparison with healthy individuals – * p <0,01;
** p <0,001.

3. Results and Discussion

The analysis of the researched indices has shown (Fig. 1) that on the stage of CPHD decompensation with HF NYHA Class III the aldosterone level increased to (197,9 ± 18,3) pg / ml vs. (56,8 ± 6,9) pg / ml in healthy individuals, so on the average on 71,3% ($p < 0,001$).

These results are consistent with the data [1, 4] on the growth of aldosterone production from RAAS activation in patients with CPHD and HF.

Along with the activation of RAAS, which was accompanied by an increase of aldosterone level, in these patients was marked an increase in blood of marker of heart failure NT-proBNP to (598,3 ± 19,1) fmol / ml vs. (95,2 ± 7,4) fmol / ml in healthy individuals, so on the average on 83,2% ($p < 0,001$), proinflammatory cytokine TNF-α to (24,8 ± 5,6) pg / ml versus a referential meaning (4,5 ± 2,1) pg / ml, so on the average on 81,8% ($p <0,001$) and apoptosis inducer Fas-Ligand to (382,6 ± 35,9) pg / ml vs. (115,9 ± 12,3) pg / ml in healthy individuals, so on the average on 69,7% ($p < 0,01$).

A clear positive correlation relationship between the increase in the blood level of aldosterone and NT-proBNP ($r = +0,73$: $p <0,01$), TNF-α ($r = +0,68$; $p = 0,02$) and FasL ($r = +0,59$; $p < 0,05$) was established during a multiple correlation analysis.

The received increase in blood concentration of TNFα with decompensated CPHD, which correlates with the survey data of K. M. Amosova and the cowriters[3], and C. T. Gan *et al*.[17] with the value of NT-proBNP, as a marker of progression of the right ventricle dilatation and dysfunction in case of the right ventricle HF.

The revealed increase in TNFα indicates the activation of cytokines in patients with COPD, which is confirmed by the results of researches of other authors[2, 13]. This in turn leads to damage of cardiomyocytes, cardiac remodeling and progression of heart failure[5, 18], which was proven in our research, as in patients with decompensated CPHD was observed HF NYHA Class III.

Increased expression of FasL in patients with decompensated CPHD indicates the activation of apoptosis of cardiomyocytes due to hypoxia in cases of CPHD as a result of COPD [10, 15].
Ambiguous results in the main and the control groups of patients were revealed during the analysis of treatment dynamics (Table 1, Fig. 2).
In particular, a combined therapy with ACE inhibitor enalapril with the angiotensin II receptor blocker candesartan provided an opportunity to reduce the concentration of aldosterone in blood (201,8 ± 15,6) pg / ml to (119,1 ± 8,3) pg / ml, so on the average to 40,1% ($p < 0,01$) in the main group.

In the control group at the end of the 6 month period was stated a lowering of aldosterone in blood from (189,4 ± 14,2) pg / ml to (147,6 ± 9,1) pg / ml, which on the average formed 22.1% ($p < 0,05$). So, with a combined RAAS blockade at the stage of formation and binding of angiotensin II with the receptors, aldosterone synthesis is reduced almost in 2 times ($p < 0,05$).

A decrease in blood concentration of marker of heart failure with NT-proBNP (603,2 ± 15,7) fmol / ml to (324,6 ± 10,5) fmol / ml, on the average on 46, 2% ($p < 0,001$), and the proinflammatory cytokine TNF-α from (26,3 ± 4,1) pg / ml to (13,6 ± 3,9) pg / ml, so on the average on 48.3% ($p < 0,001$) were stated after 6 months of treatment in the main group. A positive, but less pronounced dynamics of these indices was noticed in the control group. So, after 6 months blood levels of NT-proBNP decreased from (591,9 ± 12,6) fmol / ml to (435,7 ± 11,8) fmol / ml, representing an average of 26,4% ($p < 0.05$), and TNF-α – of (21,4 ± 3,8) pg / ml to (15,8 ± 2,5) pg / ml, so on the average to 26,1 ($p < 0,05$).

Blood level of pathological apoptosis inducer Fas-Ligand in patients of the main group

decreased from (398,5 ± 20,9) pg / ml to (204,7 ± 19,6) pg / ml, which was on the average 48.6% (p < 0,001), and the control group - from (376,9 ± 18,5) pg / ml to (245,1 ± 17,3) pg / ml, representing an average of 34,9% (p < 0,01).
Positive effects of combined use of an ACE inhibitor enalapril and the ARB candesartan were found during the analysis of the effectiveness of treatment with nonparametric statistical methods. Thus, in the main group with respect to the control of the aldosterone dynamics the Pearson criterion $\chi 2$ was 4,36 (p = 0,034), and Fisher's exact test – (p = 0,036; two-tailed); according to the NT-proBNP dynamics: the Pearson criterion $\chi 2$ – 6,35 (p = 0,011), and Fisher's exact test – (p = 0,018; two-tailed); according to the dynamics of TNF-α: the Pearson criterion $\chi 2$ - 4,19 (p = 0,040), and Fisher's exact test – (p = 0,034; two-tailed); according to the FasL dynamics: the Pearson criterion $\chi 2$ – 5,60 (p = 0,017), and Fisher's exact test – (p = 0,046; two-tailed).

Table 1: Blood levels dynamics of aldosterone, marker of heart failure NT-proBNP, a Proinflammatory Cytokine TNFα, and apoptosis inducer Fas-Ligand under the influence of ACE inhibitor Enalapril and its combination with the ARB candesartan in patients with decompensated CPHD with HF NYHA Class III, (M ± m)

Indices	The main group (n=39)				The control group (n=35)			
	Before treat-ment	After treat-ment	Δ, %	p	Before treat-ment	After treat-ment	Δ, %	p
Aldoste-rone, pg / ml	201,8 ± 15,6	119,1 ± 8,3	- 40,1 ± 7,6	p<0,01	189,4 ± 14,2	147,6 ± 9,1	- 22,1 ± 7,1	p<0,05
NT-proBNP, fmol / ml	603,2 ± 15,7	324,6 ± 10,5	- 46,2 ± 8,9	p<0,001	591,9 ± 12,6	435,7 ± 11,8	- 26,4 ± 7,3	p<0,05
TNF-α, pg / ml	26,3 ± 4,1	13,6 ± 3,9	- 48,3 ± 8,7	p<0,001	21,4 ± 3,8	15,8 ± 2,5	- 26,1 ± 6,5	p<0,05
Fas-Ligand, pg / ml	398,5 ± 20,9	204,7 ± 19,6	- 48,6 ± 9,5	p<0,001	376,9 ± 18,5	245,1 ± 17,3	- 34,9 ± 8,4	p<0,01

Notes:
1. Δ,% – ratio of final to initial values of the index in percentage terms;
2. p reliability of the difference relatively to the original value of the index.

The reduction of an average functional class NYHA In the main group from (2,5 ± 0,6) to (1,6 ± 0,4) (p <0,05) and in the control group - from (2,3 ± 0,5) to (1,7 ± 0,4) (p < 0,05) was stated during the 6-month observation period. However, 1 patient from the main group and 3 patients from the control group were hospitalized with the signs of HF decompensation during an observation period received data on more severe clinical effectiveness and positive impact on blood levels of neurohumoral mediators and cytokines during a combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan in patients with decompensated CPHD with NYHA Class III are consistent with the "CHARM-Added" trial within a multicenter, double-blind,

randomized, placebo-controlled trial Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM), which studied the effect of combined treatment with enalapril and candesartan in patients with heart failure [11].

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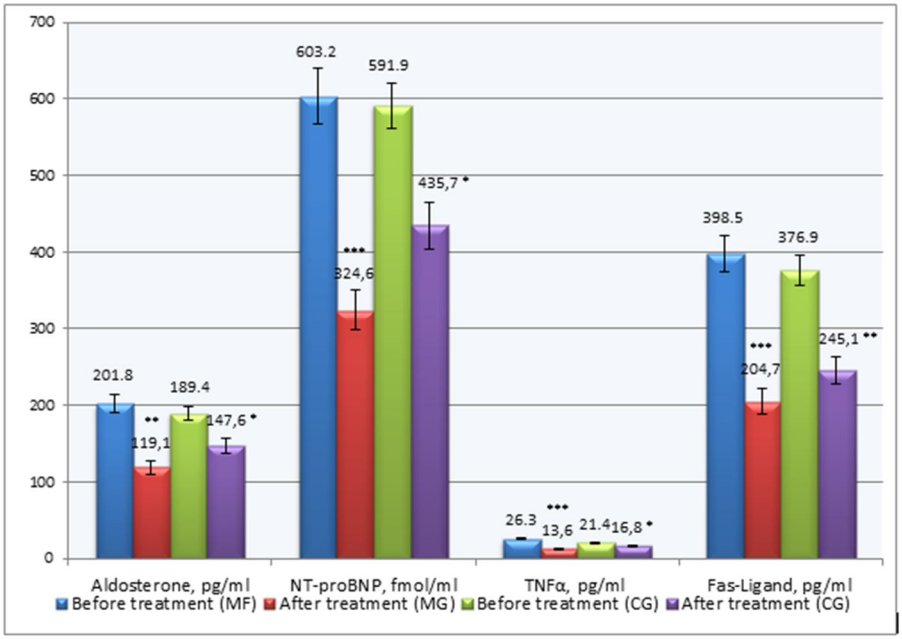

Figure 2: Blood levels dynamics of aldosterone, marker of heart failure NT-proBNP, a proinflammatory cytokine TNFα, and apoptosis inducer Fas-Ligand under the influence of ACE inhibitor enalapril and its combination with the ARB candesartan in patients with decompensated CPHD with HF NYHA Class III.

Notes: MG - the main group, CG – the control group; * p <0,05 respectively to the original value of the index; ** p <0,01 respectively to the original value of the index; *** p <0,001 respectively to the original value of the index.

None serious side effects were observed in our researches, both of the studied medicines combined well with CPHD and HF standard basic therapy.

4. Conclusions

- Chronic pulmonary heart disease on the stage of decompensation is characterized with an increased activity of RAAS, activation of cytokine system and pathological apoptosis.
- The combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan within 6 months reduces blood levels of aldosterone, a marker for heart failure NT-proBNP, a proinflammatory cytokine TNF-α and apoptosis inducer Fas-Ligand, which leads to slower progression of heart failure in patients with decompensated chronic pulmonary heart disease.
- Clinical efficacy of a prolonged combined use of ACE inhibitor enalapril with ARB candesartan against the background of a basic therapy chronic pulmonary heart disease and heart failure according to the dynamics of blood levels of aldosterone, NT-proBNP, TNF-α and FasL is higher than with the same treatment without angiotensin II receptor blocker.

4.1 Prospects for Further Research in this Direction are to clarify the relationship of blood levels of aldosterone, NT-proBNP, TNF-α and FasL with other pathogenetic factors of CPHD development, in particular, with the levels of endothelin-1, vascular endothelial growth factor and fibroblast growth factor. This will help to open a new trend in the diagnosis and treatment of chronic pulmonary heart disease.

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