The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 11-02-2013
Accepted: 15-03-2013

Vol. 2 Issue 3 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Evaluation of the Effectivness of the Angiotensin-Converting Enzyme Inhibitor Enalapril and the Angiotensin II Receptor Blocker Candesartan use in Patients with Chronic Pulmonary Heart Disease According to the Dynamics of Fibroblast Growth Factor and Pulmonary Artery Systolic Pressure

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 the angiotensin-converting enzyme (ACE) inhibitor enalapril and the angiotensin II receptor blocker (ARB) candesartan on the blood levels of basic fibroblast growth factor (bFGF) and dynamics of pulmonary artery systolic pressure (PASP) in patients with chronic pulmonary heart disease (CPHD). The study involved 282 patients with compensated and decompensated CPHD with heart failure (HF) NYHA Class II-IV, including 214 (75.9%) men and 68 (24.1%) women. The average age of men – (59.2 ± 10.8) years, women – (63.7 ± 4.5) years. It was found that the most pronounced increase of bFGF level to (63.48 ± 8.65) pg / ml versus referential value of this index (18.61 ± 4.96) pg / ml ($p < 0.001$) was observed in patients with CPHD with HF NYHA Class IV. ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the background of the basic therapy inhibit an excessive production of bFGF and progression of pulmonary arterial hypertension, which indicates the feasibility of adding them to the standard CPHD treatment. The angiotensin II receptor blocker candesartan should be added to the basic therapy in the early stages of CPHD development. A combined use of the basic therapy with ACE inhibitor enalapril and the angioten II receptor blocker candesartan is appropriate during the later stages of CPHD NYHA Class III-IV.

Keyword: Basic Fibroblast Growth Factor, Pulmonary Artery Systolic Pressure, Angiotensin-Converting Enzyme Inhibitor Enalapril, Angiotensin II Receptor Blocker Candesartan, Chronic Pulmonary Heart Disease.

1. Introduction

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (HF) are global epidemics, each affecting in excess of 10 million patients. Both conditions incur significant morbidity and mortality, and present significant challenges to healthcare providers[6,17]. Moreover, COPD and HF also frequently coexist in clinical practice as they share the same risk factors, including cigarette smoking, advanced age and systemic inflammation[4,13]. In COPD, CHF is prevalent in more than 20% of patients[8,14].

On the other hand, according to classical concepts, damage of the pulmonary heart, known as chronic pulmonary heart disease (CPHD) or cor pulmonale, eventually develops in patients with COPD. Cor pulmonale was classically defined as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs except when these

pulmonary alterations are the result of diseases that primarily affect the left side of the heart" (WHO expert committee report 1963)[16]. Since this definition does not indicate the presence of right heart failure, and since the presence of edema does not always imply underlying right heart failure in stable COPD patients, the terms cor pulmonale and right heart failure are not synonymous. Pulmonary arterial hypertension (PAH) however is always the underlying pathologic mechanism for right venrticular hypertrophy in cor pulmonale and may lead with time to right heart failure[12].

Basic fibroblast growth factor (bFGF), stored in the extracellular matrix, has been documented to have a role in vascular cell migration, endothelial and smooth-muscle cell growth, and synthesis of extracellular matrix proteins[15]. In view of their proliferative effects, these growth factors may have a pathophysiologic role in PAH. As both endothelial cell and smooth-muscle cell proliferation are present in PAH, bFGF may have a particular role because of its effects on both endothelial and smooth-muscle cells. Patients with PAH have substantial alterations in urine and plasma levels of bFGF. This molecule may have a role as a mitogenic factor in the endothelial and smooth-muscle cell proliferation seen in PAH[1,7].

The effect of angiotensin-converting enzyme (ACE) inhibitors enalapril, the angiotensin II receptor blocker candesartan and their combined use on bFGF blood level in patients with CPHD with various options of course is not clear.

1.1 The aim of research

To study the influence of a prolonged use of ACE inhibitor enalapril and the ARB candesartan on the blood levels of basic fibroblast growth factor and dynamics of pulmonary artery systolic pressure (PASP) in patients with chronic pulmonary heart disease.

2. Materials and Methods

The study involved 282 patients with CPHD caused by COPD. Including 214 (75.9%) men and 68 (24.1%) women. The average age of men was (59.2 ± 10.8) years, the average age of women was (63.7 ± 4.5) 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)[5].

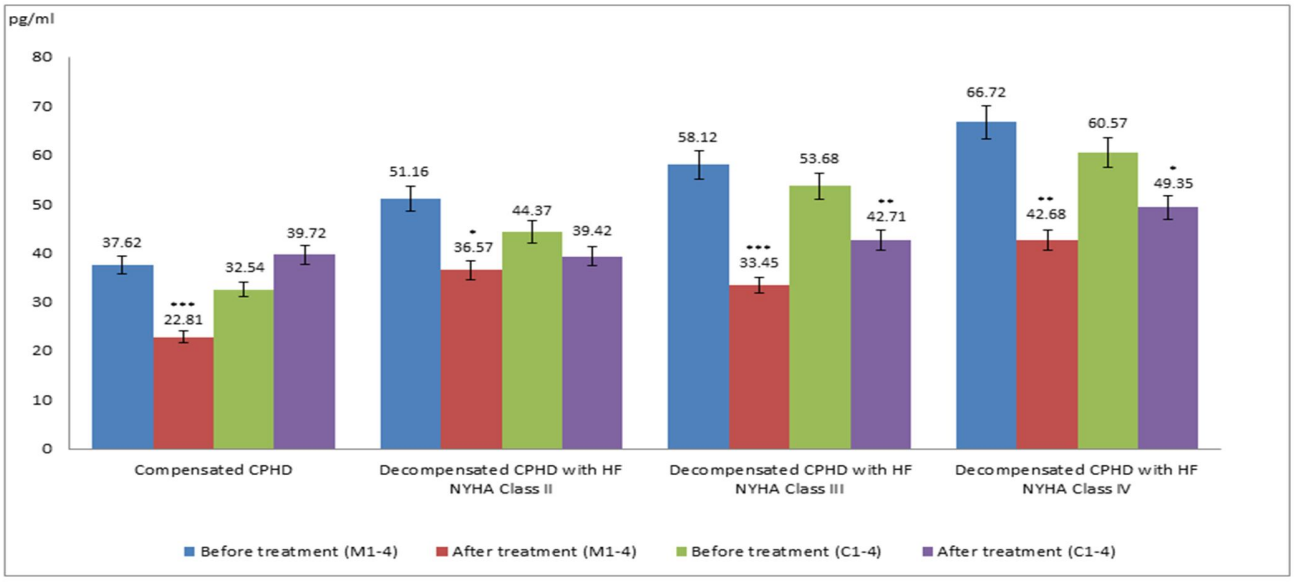
Heart failure NYHA II – IV Class was verified in all patients with decompensated CPHD under Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) of the European Society of Cardiology[9].

All patients were divided into the following groups: 1 - 55 patients with compensated CPHD, 2 - 69 patients with decompensated CPHD with heart failure NYHA Class II; III - 74 patients with decompensated CPHD with HF NYHA Class III; 4 - 84 patients with decompensated CPHD with HF NYHA Class IV, to assess the relationship between blood levels of bFGF and the stage of heart failure.

All patients received a basic COPD and 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) [5]; 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[9].

All patients were divided into subgroups to evaluate the effectiveness of treatment, depending on the composition of a pharmacotherapeutic complex. A main group was divided as follows: the first (M_1) - 29 patients with compensated CPHD that were treated with the basic therapy (excluding ACE inhibitors) and the angiotensin II receptor blocker candesartan (BT + C); the second (M_2) - 36 patients with decompensated CPHD and HF NYHA Class II , who received a basic therapy (excluding ACE inhibitor) and candesartan (BT + C); the third (M_3) - 39 patients with decompensated CPHD with HF NYHA Class III in which, on the background of the basic therapy that included ACE inhibitor enalapril, the angiotensin II receptor blocker candesartan was used (BT + E + C); the fourth

(M_4) subgroup comprised 43 patients with decompensated CPHD with HF NYHA Class IV, which also received the basic therapy which included enalapril and candesartan (BT + E + C).



Notes: 1. M_{1-4} – the main subgroups; 2. C_{1-4} – the control subgroups; credibility of difference: * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$; in comparison with baseline values.

Fig 1: Dynamics of bFGF serum levels under the influence of various versions of pharmacotherapy in patients with CPHD.

The results were compared with those in a control group which comprised 135 patients who were divided into subgroups: the first (C_1) - 26 patients with compensated CPHD who were treated with the basic therapy without ACE inhibitor (BT); the second (C_2) - 33 patients with decompensated CPHD and HF NYHA Class II; the third (C_3) subgroup included 35 patients with decompensated CPHD and HF NYHA Class III; the fourth -(C_4) included 41 patients with decompensated CPHD and HF NYHA Class IV. All the patients from the control subgroups with CPHD and HF NYHA Class II - IV received the basic therapy that included ACE inhibitor enalapril (BT + E).

The researched drugs, ACE inhibitor enalapril (Enap, "KRKA", Slovenia) and the angiotensin II receptor blocker candesartan (candesartan, "Ranbaxy", India-USA-Canada), were administered with the help of the titration method, respectively, from 2.5 mg / day and 4 mg / day to the maximum tolerated dose. Moreover, in the case of a combined use of enalapril with candesartan, titration ACE inhibitor enalapril was performed first, and subsequently under the condition of a stable hemodynamics, the titration of the angiotensin II receptor blocker candesartan was started.

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.

The indices of 27 healthy individuals, at (28.4 ± 2.9) years of age served as criterion standard.

The blood level of bFGF was determined with the help of an immunoenzyme method using the test system made by the company "Biosource" (USA). Doppler determination of pulmonary artery systolic pressure (PASP) was performed to assess the dynamics of PAH by a standard method. The above mentioned tests were performed at the beginning of the research and after 6 months of the treatment.

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 odds ratio (OR); 95% Confidence Intervals (95% CI); χ^2 – Pearson's chi-squared test; the absolute risk reduction (ARR), and the relative risk reduction (RRR); and the number needed to treat (NNT).

3. Results and Discussion

We began the analysis of the results with the assessment of bFGF level in hemocirculation in different variants of CPHD course. It turned out that the expression of bFGF increases in the early stages of CPHD formation - compensated and decompensated CPHD with HF NYHA Class II. Thus, in the presence of compensated CPHD the blood level of bFGF in 41 patients (74.5%) was (35.47 ± 5.84) pg / ml, and with decompensated CPHD with HF NYHA Class II in 54 (78.3%) patients – (48.29 ± 6.73) pg / ml vs. (18.61 ± 4.96) pg / ml in healthy individuals ($p < 0.01$). The largest concentrations of FGF in blood was noticed in 62 (83.8%) patients – (55.36 ± 9.20) pg / ml with decompensated CPHD with HF NYHA Class III and 78 (92.8%) patients – (63.48 ± 8.65) pg / ml with HF NYHA Class IV vs. the referential meaning of this value (18.61 ± 4.96) pg / ml ($p < 0.001$). The bFGF levels were slightly increased or did not exceed normal values in the remaining patients.

These results are consonant with the data on the dependance of over-expression of bFGF, which leads to a significant induction of neoangiogenesis and interstitial myocardial fibrosis, and the progression of heart failure in patients with decompensated CPHD due to COPD[2,7,11].

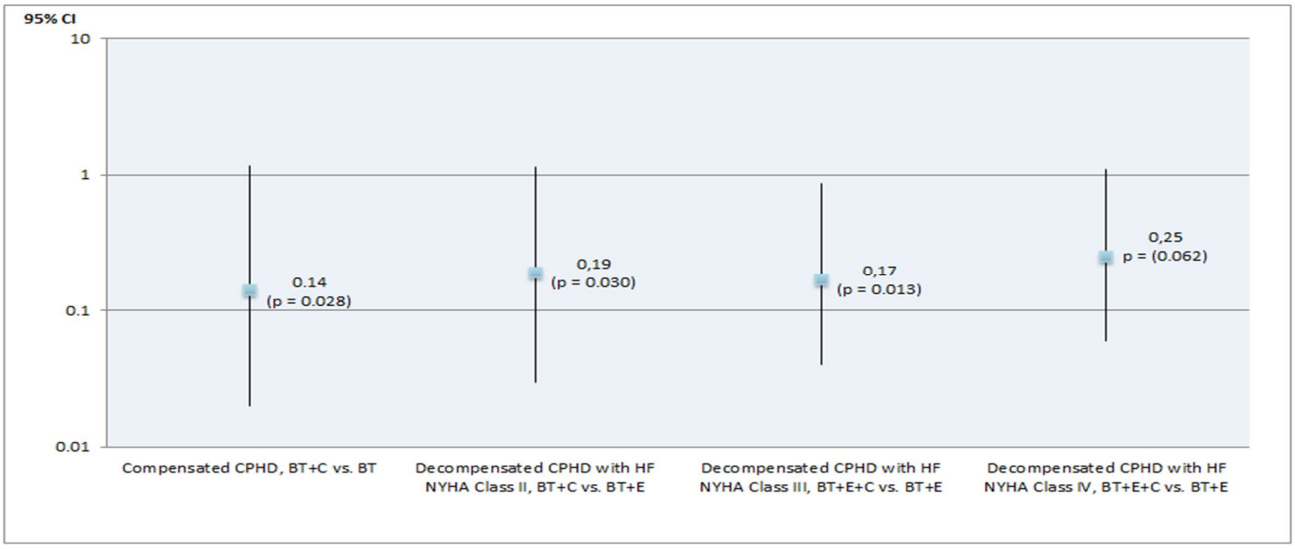
The analysis of bFGF levels dynamics under the influence of various versions of pharmacotherapy (Fig. 1) revealed that the use of candesartan in patients with compensated CPHD against the background of the basic therapy within 6 months contributed to a significant reduction of bFGF concentration – from (37.62 ± 4.36) pg / ml to (22.81 ± 3.92) pg / ml, which on the average was 39.36% ($p < 0.001$). At the same time, FGFb level didn't change in the control subgroup – (32.54 ± 5.01 pg / ml) in the initial state and (39.72 ± 4.63) pg / ml in 6 months ($p > 0.05$). Less striking was the dynamics in decompensated CPHD with HF NYHA Class II, when bFGF concentration in blood after treatment in the main subgroup decreased from (51.16 ± 5.24) pg / ml to (36.57 ± 4.95 pg / ml), so on the average on 28.51% ($p < 0.05$), whereas in the control subgroup a tendency to decrease from (44.37 ± 4.38) pg / ml to (39.42 ± 3.69) pg / ml ($p > 0,05$) was observed.

Under the condition of a combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the background of the basic therapy in patients with decompensated CPHD with HF NYHA Class III a significant reduction of bFGF level was observed – from (58.12 ± 7.83) pg / ml to (33.45 ± 8.61) pg / ml, which on the average was 42.44% ($p < 0.001$), against the decrease from (53.68 ± 7.34) pg / ml to (42.71 ± 8.06) pg / ml in the control subgroup, which means on 20.43% ($p < 0.01$).

Less pronounced dynamics was observed with decompensated CPHD with HF NYHA Class IV, when under the influence of the basic therapy with enalapril and candesartan the content of bFGF serum decreased from (66.72 ± 8.24) pg / ml to (42.68 ± 7.53) pg / ml, which comprised the average of 36.03% ($p < 0.01$); while under the influence of the basic therapy with enalapril – from (60.57 ± 8.93) pg / ml to (49.35 ± 7.61) pg / ml, so on 18.52% ($p < 0.05$).

The prevalence of positive results over negative was observed after the treatment with ACE inhibitor enalapril and its combination with the angiotensin II receptor blocker candesartan on the background of the basic therapy during the analysis of the odds ratio of unfavorable or favorable treatment effects under the influence of

various pharmacological systems according to the dynamics of bFGF content in blood (Fig. 2, Table 1). In particular, in a case of compensated CPHD and its treatment with the basic therapy with candesartan the odds ratio was less than one (OR = 0.14; 95% CI 0.02 – 1.16; χ^2 = 3.60; p = 0.028).The OR dynamics was similar in patients with decompensated CPHD and HF NYHA Class II, in which candesartan was used on the background of the basic therapy (OR = 0.19; 95% CI 0.03 – 1.14; χ^2 = 3.48; p = 0.030).



Note: 1. OR – the odds ratio of unfavorable or favorable treatment effects; 2. 95% CI – 95% confidence interval; 3. p – the reliability coefficient; 4. BT – basic therapy; 5. E – enalapril; 6. C – candesartan.

Fig 2: The odds ratio of unfavorable or favorable treatment effects in patients with CPHD using ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan according to bFGF dynamics.

The most pronounced inhibition of excessive production of bFGF was observed in patients with decompensated CPHD with HF NYHA Class III, which undergo the basic therapy treatment with enalapril and candesartan (OR = 0.17; 95% CI 0.04 – 0.86; χ^2 = 4.91; p = 0.013). So, in other words, dual blockade of renin-angiotensin-aldosterone system (RAAS) is highly effective, as the OR indicates a clear positive outcome. Slightly less effective was the treatment of patients with decompensated CPHD with severe HF NYHA Class IV (OR = 0.25; 95% CI 0.06 – 1.10; χ^2 = 3.47; p = 0.062) with a similar pharmacological complex (BT + E + C).

The results of ARR, RRR and NNT (Table 2) proved to be important. It was found that candesartan on the background of the basic therapy significantly reduces the absolute risk of the adverse effects of compensated CPHD (ARR = -0.44; 95% CI -0.85 – -0.03) and decompensated CPHD with HF NYHA Class II (ARR = -0.38; 95% CI -0.76 – -0.01) treatment. High specificity of positive dynamics of the absolute risk (ARR = -0,39; 95% CI -0.72 – -0.07) was marked in the presence of decompensated CPHD with HF NYHA Class III and its treatment with the combinaton of candesartan and enalapril on the background of the basic therapy. The positive dynamics of the ARR (ARR = -0.32; 95% CI -0.65 – 0.02) was also observed in the case of decompensated CPHD with HF NYHA Class IV.

Table 1: Effect of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the odds ratio of unfavorable or favorable treatment effects in patients with CPHD according to the dynamics of bFGF level in blood

Subgroups of patients	OR	95% CI	χ^2	p
Compensated CPHD; BT+C (M_1 – n=29 vs. C_1 – n=26)	0.14	0.02 – 1.16	3.60	0.028
Decompensated CPHD with HF NYH Class II; BT+C (M_2 – n=36 vs C_2 – n=33)	0.19	0.03 – 1.14	3.48	0.030
Decompensated CPHD with HF NYH Class III; BT+E+C (M_3 – n=39 vs. C_3 – n=35)	0.17	0.04 – 0.86	4.91	0.013
Decompensated CPHD with HF NYH Class IV; BT+E+C (M_4 – n=43 vs C_4 – n=41)	0.25	0.06 – 1.10	3.47	0.062

Notes: 1 OR – the odds ratio of unfavorable or favorable treatment effects; 2. 95% CI – 95% confidence interval; 3. χ^2 – Pearson's chi-squared test; 4. p – the reliability coefficient; 5. M_{1-4} – the main subgroups; 6. C_{1-4} – the control subgroups; 7. BT – basic therapy; 8. E – enalapril; 9. C – candesartan.

The RRR (relative risk reduction) was better with compensated CPHD under the influence of the basic therapy with candesartan (RRR = 0.33; RRR,% = -66.7%; 95% CI 0.09 – 1.23). Less pronounced RRR was observed in case of decompensated CPHD with HF NYHA Class II (RRR = 0.39; RRR,% = -60.7%; 95% CI 0.13 – 1.15). The RRR (RRR = 0.36; RRR,% = -63.9%; 95% CI 0.14 – 0.95) was significant in the presence of a combined RAAS blockade with candesartan and enalapril on the background of the basic therapy in patients with decompensated CPHD with HF NYHA Class III. The least effective RRR was in patients with CPHD with HF NYHA Class IV (RRR = 0.46; RRR,% = -53.7%; 95% CI 0.20 – 1.09).

The dynamics of the NNT value was similar to the changes of the ARR and RRR values. In particular, the lowest value of the NNT (NNT = 2,25; 95% CI 1.16 – 29.57) was in the group of patients with compensated CPHD which were treated with candesartan against the background of the basic therapy. The use of the basic therapy with candesartan also had a positive influence on the NNT value (NNT = 2.6; 95% CI 1.31 – 30.24) in patients with decompensated CPHD with HF NYHA Class II.

The NNT value (NNT = 2.5; 95% CI 1.38 – 15.07) was reasonably low in case of a combined RAAS blockade with enalapril and candesartan against the background of the basic therapy in patients with decompensated CPHD with HF NYHA Class III.

Table 2: Effect of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the risk values of the adverse effects of treatment in patients with CPHD according to the dynamics of bFGF level in blood

Subgroups of patients	ARR	95% CI	RRR	RRR, %	95% CI	NNT	95% CI
Compensated CPHD; BT+C (M_1 – n=29 vs C_1 – n=26)	-0.44	-0.85 – -0.03	0.33	-66.7	0.09 – 1.23	2.25	1.16 – 29.57
Decompensated CPHD with HF NYHA Class II; BT+C (M_2 – n=36 vs C_2 – n=33)	-0.38	-0.76 – -0.01	0.39	-60.7	0.13 – 1.15	2.6	1.31 – 30.24
Decompensated CPHD with HF NYHA Class III; BT+E+C (M_3 – n=39 vs C_3 – n=35)	-0.39	-0.72 – -0.07	0.36	-63.9	0.14 – 0.95	2.5	1.38 – 15.07
Decompensated CPHD with HF NYHA Class IV; BT+E+C (M_4 – n=43 vs C_4 – n=41)	-0.32	-0.65 – 0.02	0.46	-53.7	0.20 – 1.09	3.1	1.55 – 44.32

Notes: 1. ARR – the absolute risk reduction of adverse effects of treatment; 2. RRR – the relative risk reduction of adverse effects of treatment; 3. NNT – number of patients needed to treat; 4. 95% CI – 95% confidence interval; 5. M_{1-4} – the main subgroups; 6. C_{1-4} – the control subgroups; 7. BT – basic therapy; 8. E – enalapril; 9. C – candesartan.

The NNT value was the highest in the case of a severe CPHD decompensation with HF NYHA Class IV even with the combined use of enalapril and candesartan (NNT = 3.1; 95% CI 1.55 – 44.32).

Taking into account the data on the ability of angiotensin II receptor blocker to activate the expression of bFGF [1, 3] in patients with COPD, we can explain obtained positive effects of ACE inhibitor enalapril, the angiotensin II receptor blocker candesartan and their combination on bFGF level in patients with CPHD.

Lowering of bFGF level in blood was accompanied by a reduction of PAH. The dynamics of the PASP value has proved this. Thus, in patients of the main subgroup with compensated CPHD PASP value has decreased after 6 months of treatment from (68.45 ± 3.27) mmHg to (42.71 ± 3.46) mm Hg, which comprised the average of 37,6% ($p < 0.001$), and in the control subgroup – from (63.92 ± 4,08) mm Hg to (51.67 ± 3.74), that represented the average of 19.1% ($p < 0.05$), so almost 2 times smaller. More pronounced PASP dynamics was in patients with decompensated CPHD with HF NYHA Class III under the influence of the combined use of ACE inhibitor enalapril on the angiotensin II receptor blocker candesartan against the background of the basic therapy, in comparison with the same treatment without candesartan. In particular, PASP decreased from (76.83 ± 5.31) mmHg to (51.67 ± 4,23) mm Hg, which comprised an average 32.7% ($p < 0.001$) in patients of the main subgroup after 6 months of treatment, and in the control subgroup – from (72.59 ± 4.86) mmHg to (53.62 ± 4.95), that represented the average of 26.1% ($p < 0.01$).

Taking into account the role of an elevated bFGF level in the pathogenesis of PAH in patients with COPD[1,7], this effect can have a positive impact on the development and progression of right ventricular HF in patients with CPHD.

Use of the angiotensin II receptor blocker candesartan and especially its combination with ACE inhibitor enalapril has resulted in improvement of the patients' clinical condition and reduction of the functional class of heart failure. So, in 35 (97.2%) patients of the main subgroup with decompensated CPHD and Stage I CHF was stated a decrease of the functional class from NYHA Class II to Class I after 6 months of treatment, while similar dynamics was observed in 32 (96.9%) patients from the control subgroup. A positive dynamics was observed after the treatment in more severe cases of heart failure, when was noticed the reduction from Class III to Class II NYHA in 34 (87.2%) patients of the main subgroup, and in 5 (12.8%) cases the reduction reached NYHA Class I. The severity of CHF symptoms has reduced from Class III to Class II in 31 (88.6%) patients from the control subgroup and in 3 (8.5%) patients NYHA Class I. A positive trend has appeared in cases of a very severe heart failure, but lower class than NYHA Class III was not achieved in any case. Specifically, after treatment in 42 (97.7%) patients of the main subgroup was notice a shift from NYHA Class IV to Class III, and in the control subgroup this dynamic was marked in 39 (95.1%) patients. However, 1 (2.3%) patient from the main subgroup with HF NYHA Class IV and three patients from the control subgroups [1 (2.8%) with HF NYHA Class III and 2 (4.9%) patients with HF NYHA Class IV were hospitalized due to the appearance of heart failure decompensation signs during the observation period.

In addition to reduction of the subjective symptoms of heart failure (shortness of breath, palpitations), the reduction of heart rate and a modest reduction in blood pressure were marked in both the main and control groups on the background of the basic therapy. The most pronounced dynamics of these parameters was observed in the case of a combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the background of the basic therapy, and this was not accompanied by deterioration of the patients' clinical condition.

There were no cases of hospital or out-of-hospital death during the entire period of observation and treatment.

Received data on more severe clinical effectiveness and positive impact on blood levels

of bFGF during a combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan in patients with decompensated CPHD 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[10].

Also, the results on the positive effect of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on bFGF level and CPHD course in patients with COPD are consistent with findings that angiotensin-converting enzyme inhibitors, and the angiotensin -receptor blockers may reduce the morbidity and mortality of the patients with COPD[17].

No serious side effects were noticed in any of our researches, both studied medications combined well with a standard basic therapy.

4. Conclusions

1. Production of fibroblast growth factor depends on the degree of compensation of CPHD and the HF stage. The most pronounced increase of bFGF level in blood was observed in patients with decompensated CPHD with HF NYHA Class IV.
2. ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the background of the basic therapy inhibit an excessive production of bFGF and progression of pulmonary arterial hypertension, which indicates the feasibility of adding them to the standard CPHD treatment.
3. The absolute and relative risk reduction of unfavorable course of CPHD under the influence of various versions of pharmacotherapy with the use of ACE inhibitor enalapril and the candesartan II receptor blocker is reliable and sufficiently specific.
4. On early stages of CPHD development one should add the angiotensin II receptor blocker candesartan to the basic therapy. Combined use of the basic therapy with ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan is appropriate at the later stages of CPHD with HF NYHA Class III - IV.

4.1 Prospects for Further Research in this Direction: are to clarify the relationship of bFGF level in blood with other pathogenetic factors of CPHD development, including the levels of endothelin-1, vascular endothelial growth factor, apoptosis inducer Fas-Ligand, and aldosterone. This will open a new trend in the diagnosis and treatment of CPHD.

References

1. Benisty JI, McLaughlin VV, Landzberg MJ, Rich JD, Newburger JW, Rich S, Folkman J. Elevated basic fibroblast growth factor levels in patients with pulmonary arterial hypertension. Chest. 2004 Oct;126 (4):1255-61.
2. Booz GW, Baker KM. Molecular signalling mechanisms controlling growth and function of cardiac fibroblasts. Cardiovasc Res 1995; 30: 537–543.
3. Bouzegrhane F, Thibault G. Is angiotensin II a proliferative factor of cardiac fibroblasts? Cardiovasc Res 2002; 53: 304–312.
4. Chhabra SK, Gupta M. Coexistent chronic obstructive pulmonary diseaseheart failure: mechanisms, diagnostic and therapeutic dilemmas. Indian J Chest Dis Allied Sci 2010; 52: 225-38.
5. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease: (Updated 2013) [Electronic Resource] – Mode of access: http:// www.goldcopd.org
6. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009; 11: 130-9.
7. Kranenburg AR, De Boer WI, Van Krieken JH, et al. Enhanced expression of fi broblast growth factors and receptor FGFR-1 during vascular remodeling in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol, 2002, 27: 517–25.
8. Lainscak M, Hodoscek LM, Düngen HD, Rauchhaus M, Doehner W, Anker SD, et al. The burden of chronic obstructive pulmonary disease in patients hospitalized with heart

failure. Wien Klin Wochenschr 2009; 121: 309-13.
9. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-1847.
10. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. (2003). Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 362 (9386): 767-71.
11. Sabbah HN, Sharov VG, Lesch M, Goldstein S . Progression of heart failure: a role for interstitial fibrosis. Mol Cell Biochem 1995;147:29-34.
12. Shujaat A, Minkin R, and Eden E. Pulmonary hypertension and chronic cor pulmonale in COPD. Int J Chron Obstruct Pulmon Dis 2007 September; 2 (3): 273–282.
13. Suskovic S, Kosnik M, Lainscak M. Heart failure and chronic obstructive pulmonary disease: Two for tea or tea for two? World J Cardiol 2010; 2: 305-7.
14. Ukena C, Mahfoud F, Kindermann M, Kindermann I, Bals R, Voors AA, et al. The cardiopulmonary continuum systemic inflammation as 'common soil' of heart and lung disease. Int J Cardiol 2010; 145: 172-6.
15. Vlodavsky I, Folkman J, Sullivan R, et al. Endothelial cellderived basic fibroblast growth factor: synthesis and deposition into subendothelial extracellular matrix. Proc Natl Acad Sci USA 1987; 84: 2292–2296.
16. World Health Organization. Chronic cor pulmonale. Report of an expert committee. Circulation 1963; 27: 594–615.
17. Zeng Q, Jiang S. Update in diagnosis and therapy of coexistent chronic obstructive pulmonary disease and chronic heart failure. J Thorac Dis. 2012; 4 (3): 310-315.