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Evaluation of the Effect of Angiotensin-Converting Enzyme Inhibitors and the Angiotensin II Receptor Blockers on the Dynamics of Mitogenic Growth Factors, Apoptosis Inducers and Pulmonary Artery Systolic Pressure in Patients with Chronic Pulmonary Heart Disease

Vitaliy Seredyuk[1*]

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

The dynamics of mitogenic growth factors was investigated, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and apoptosis inducer Fas-Ligand (FasL), and the level of pulmonary artery systolic pressure (PASP) under the influence of angiotensin-converting enzyme (ACE) enalapril, and the angiotensin II receptor blocker (ARB) candesartan and their combined use in patients with chronic pulmonary heart disease(CPHD). The study involved 282 patients with CPHD, including 55 (19.5%) with compensated and 227 (80.5%) with decompensated CPHD and chronic heart failure (CHF) NYHA Class II-IV. It was found that ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan reduce levels of mitogenic growth factors bFGF, VEGF, apoptosis inducer Fas-Ligand, and PASP in patients with CPHD. Clinical efficacy of long-term (over 6 months) combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the background of a basic therapy in patients with decompensated CPHD and CHF NYHA Class III - IV judging by the dynamics of bFGF, VEGF, FasL , and PASP levels is more pronounced, than during the same treatment but without the angiotensin II receptor blocker.

Keyword: Chronic Pulmonary Heart Disease, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, Basic Fibroblast Growth Factor, Vascular Endothelial Growth Factor, Apoptosis Inducer Fas-Ligand, Pulmonary Artery Systolic Pressure.

1. Introduction

Over the last decade there has been a significant increase in the incidence and prevalence of chronic obstructive pulmonary disease (COPD), and mortality due to the development of complications, including chronic pulmonary heart disease (CPHD)[4,5].

According to the classical concept CPHD is formed under the influence of pulmonary arterial hypertension (PAH)[10,14].

At the same time, basic fibroblast growth factor (bFGF) has a proliferative effect and can be a pathophysiological factor of PAH formation and pulmonary vascular remodeling in patients with COPD[2,7].

Another mitogenic factor - vascular endothelial growth factor (VEGF) is important in the pathogenesis of PAH. It is proven that VEGF and its receptors are involved in the development of abnormal pulmonary vascular remodeling and in the increase of pulmonary resistance in patients with COPD[6]. Synergism between the expression of bFGF and VEGF, which causes the induction of angiogenesis, was also established[12].

Apoptosis inducer Fas-Ligand plays an important role in the development of CPHD along with the mentioned stimulants. The negative prognosis of CPHD in case of COPD is associated with activation of apoptosis of alveolar cells[1] and cardiomyocytes[3,4], the inducer of which is FasL[11].

The above-mentioned mechanisms lead to remodeling of the right heart and the progression of chronic heart failure (CHF) in patients with COPD[4,13].

Thus, overproduction of mitogenic factors bFGF,VEGF, and apoptosis inducer Fas-Ligand is observed in patients with CPHD as a result of COPD. One can assume that the containment of their excessive activity can improve the effectiveness of treatment of such patients.

1.1 The aim of Research

To assess the dynamics of the levels of mitogenic growth factors bFGF, VEGF, and apoptosis inducer Fas-Ligand, and PASP under the influence of angiotensin-converting enzyme (ACE) inhibitor enalapril, and the angiotensin II receptor blocker candesartan, and their combined use in patients with CPHD.

2. Materials and Methods

282 patients with CPHD due to COPD of II-IV stages were examined, including 55 (19.5%) with compensated and 227 (80.5%) with decompensated CPHD. Among the 214 surveyed patients (75.9%) were men and 68 (24.1%) women. The average age of the men was (59.2 ± 10.8) years, of the women – (63.7 ± 4.6) years.

Diagnosis 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], and CPHD - on the basis of the WHO criteria (1961)[14].

Diagnosis chronic heart failure and a functional class according to NYHA were established on the basis of Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012) of the European Society of Cardiology[8].

All the patients received a standard COPD treatment of[5] and a standard CPHD therapy[8].

Randomization of the patients was carried out taking into account the nature of the drug therapy, the degree of CPHD compensation and the class of CHF. The main group included 147 patients with CPHD. They were divided into subgroups: the first (O1) - 29 patients with compensated CPHD that were treated according to the scheme: basic therapy + candesartan (BT + C); the second (O2) - 36 patients with decompensated CPHD and CHF NYHA Class II, which also received candesartan in addition to the basic treatment (BT + C); the third (O3) subgroup - 39 patients with decompensated CPHD and CHF NYHA Class III, in which on the background of the basic therapy enalapril and candesartan (BT + E + C) were used; 43 patients with decompensated CPHD and CHF NYHA Class IV, which received the basic therapy with candesartan and enalapril (BT + E + C) composed the fourth (O4) subgroup. Gained results were compared with those of the control group that consisted of 135 patients, which were divided into the following subgroups: the first (K1) consisted of 26 patients with compensated CPHD, who received only the basic therapy (BT); the second (K2) comprised 33 patients with decompensated CPHD and CHF NYHA Class II, who were treated with enalapril and the basic therapy (BT + E); the third (R3) subgroup included 35 patients with decompensated CPHD and CHF NYHA Class III, in which was used enalapril on the background of the basic therapy(BT + E); and the fourth (K4) subgroup included 41 patients with decompensated CPHD and CHF NYHA Class IV, in which basic therapy and enalapril (BT + E) were used.

The researched drugs, ACE inhibitor enalapril (Enap, “KRKA”, Slovenia) and the angiotensin II

receptor blocker candesartan (Candesar, "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.

Determination of level in blood aldosterone ("DSL", USA), bFGF ("Biosource", USA), VEGF ("Cytimmune", USA) and apoptosis inducer Fas-Ligand ("Diaclone", USA) was performed using an immunoenzyme method.

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 ("StatSoft, Inc.", USA).

3. Results and Discussion

The analysis of bFGF levels under the influence of various versions of pharmacotherapy (Tab. 1) helped us to reveal 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 and represented (32.54 ± 5.01 pg / ml) in the initial state and (39.72 ± 4.63) pg / ml after 6 months of treatment ($p > 0.05$). Less striking was the dynamics in patients with decompensated CPHD with CHF NYHA Class II, when bFGF concentration in blood after the treatment in the main subgroup decreased from (51.16 ± 5.24) pg / ml to (36.57 ± 4.95 pg / ml), so by an average of 28.51% ($p < 0.05$), whereas in the control subgroup it didn't change significantly ($p>0,05$) .

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 CHF 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 CHF 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% ($p < 0.05$).

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

The results show that combination of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan reduced the level of bFGF serum more effectively than monotherapy with ACE inhibitor.

Table 1: The influence of ACE inhibitor enalapril, the angiotensin II receptor blocker candesartan, and their combined use on the dynamics of mitogenic growth factors bFGF, VEGF, and apoptosis inducer FasL in patients with CPHD.

Groups	bFGF, pg/ml				VEGF, pg/ml				FasL, pg/ml			
	The main group		The control group		The main group		The control group		The main group		The control group	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Compensated CPHD; BT+C (M1 – n=29 vs C1 – n=26)	37.62± 4.36	22.81± 3.92***	32.54± 5.01	39.72±4.63	21.47± 3.26	13.54± 1.98*	18.52± 2.81	16.75±1.63	283.15± 17.43	176.92± 15.41***	247.63± 13.82	194.35± 12.94**
Decompensated CPHD with CHF NYHA Class II; BT+C (M2 – n=36 vs C2 – n=33)	51.16± 5.24	36.57± 4.95*	44.37± 4.38	39.42±3.69	22.58± 2.61	15.86±3.13*	20.97± 3.45	17.14±2.86	323.68± 27.54	210.71±25.98**	305.82± 31.46	194.38±29.61**
Decompensated CPHD with CHF NYHA Class III; BT+E+C (M3 – n=39 vs C3 – n=35)	58.12± 7.83	33.45± 8.61***	53.68± 7.34	42.71±8.06**	33.40± 2.59	22.97±2.83**	31.23± 3.14	24.52±2.65*	398.52± 20.94	204.75±19.61***	376.94± 18.56	245.15±17.32**
Decompensated CPHD with CHF NYHA Class IV; BT+E+C (M4 – n=43 vs C4 – n=41)	66.72± 8.24	42.68± 7.53	60.57± 8.93	49.35±7.61*	24.63± 3.18	16.39±2.76***	21.82± 2.27	15.35±2.69**	282.67± 29.38	194.53±24.18**	263.58± 26.43	187.25±26.71*

Note: 1. O1-4 – the subgroups of the main group; **2.** K1-4 – the subgroups of the control group; **3.** p - the reliability coefficient:*p<0,05;**p<0,01;***p<0,001.

The analysis of the dynamics of VEGF (Table 1) showed that the expression of VEGF decreased from (21.47 ± 3.26) pg / ml to (13.54 ± 1,98) m / ml, by an average of 36.94% ($p < 0.05$), in patients with compensated CPHD which received the angiotensin II receptor blocker candesartan on the background of the basic therapy. At the same time such dynamics was inaccurate in the control subgroup ($p > 0.1$).The blood level of VEGF decreased from (22.58 ± 2.61) pg / ml to (15.86 ± 3.13) pg / ml, by an average of 29.76% ($p < 0.05$), in the patients of the main subgroup with decompensated CPHD and CHF NYHAClass II. At the same time, a tendency of VEGF decrease - from (20.97 ± 3.45) pg / ml to (17.14 ± 2.86) pg / ml, so by an average of 18.26% ($p > 0.05$), was only marked in the patients of the control subgroup. The blood level of VEGF decreased from (33.40 ± 2.59) pg / ml to (22.97 ± 2.83) pg / ml, by an average of 31.22% ($p < 0.01$), in cases of decompensated CPHD with CHF NYHA Class III in the main

subgroup; while in the control subgroup it decreased from (31,23 ± 3,14) pg / ml to (24,52 ± 2,65) pg / ml, by an average of 21,48% ($p < 0,05$). The same dynamic was marked in the case of decompensated CPHD with CHF NYHA Class IV. Thus, a significant decrease of the VEGF level from (24.63 ± 3.18) pg / ml to (16.39 ± 2.76) pg / ml, by an average of 33.45% ($p < 0.001$), was observed in the main subgroup; while in the control subgroup it decreased from (21.82 ± 2.27) pg / ml to (15.35 ± 2.69) pg / ml, by an average of 29.65% ($p < 0.01$).

In this way the combined use of candesartan and enalapril in patients with decompensated CPHD significantly inhibits the formation of VEGF .

Taking into account the data that VEGF and its receptors are involved in the development of abnormal pulmonary vascular remodeling and the increase of pulmonary resistance in patients with COPD[6], this effect of therapy with ACE inhibitors and the angiotensin II receptor blocker is positive in cases of CPHD.

The analysis of the FasL dynamics under the influence of treatment (Table 1) showed that in the patients of the main subgroup with compensated CPHD the serum level of FasL decreased from (283.15 ± 17.43) pg / ml to (176.92 ± 15.41) pg / ml ($p < 0.001$), by an average of 37.77%, and in the control subgroup - from (247.63 ± 13.82) pg / ml to (194.35 ± 12.94) pg / ml, by an average of 21.52% ($p < 0.01$).

The blood level of FasL decreased from (323.68 ± 27.54) pg / ml to (210.71 ± 25.98) pg / ml, by an average of 34.90% ($p < 0.01$), in main subgroup; while in the control subgroup - from (305.82 ± 31.46) pg / ml to (194.38 ± 29.61) pg / ml, by an average of 36.43% ($p < 0.01$), in the case of decompensated CPHD with CHF NYHA Class II after 6 months of treatment. At the same time, significant differences regarding the severity of FasL reduction were not detected in both groups ($p > 0.1$).

More pronounced dynamics was observed in the case of the combined use of ACE inhibitor enalapril and the angiotensin II receptor candesartan in patients with decompensated CPHD with CHF NYHA Class III. In this case the level of apoptosis inducer Fas-Ligand decreased from (398.52 ± 20.94) pg / ml to (204.75 ± 19.61) pg / ml, by an average of 48.62% ($p < 0.001$),in the patients of the main group; while in the control group - from (376.94 ± 18.56) pg / ml to (245.15 ± 17.32) pg / ml, by an average of 34.96% ($p < 0.01$).

In the case of expressed decompensation of CPHD with CHF NYHAClass IV in the main subgroup under the influence of a 6-month treatment with the pharmacotherapeutic complex (BT + E + C) the level of FasL decreased from (282.67 ± 29.38) pg / ml to (194.53 ± 24.18) pg / ml, by an average of 31.18% ($p <0.01$), and in the control subgroup - from (263.58 ± 26.43) pg / ml to (187.25 ± 26.71) pg / ml, by an average of 28.95% ($p < 0.05$).

There are some records which show that the negative prognosis of CPHD in the case of COPD is associated with activation of apoptosis of alveolar cells[1] and cardiomyocytes[3,4], the inducer of which is FasL[11].

The received results demonstrate the ability of ACE inhibitor enalapril, the angiotensin II receptor blocker candesartan, and their combination to reduce the expression of apoptosis inducer Fas-Ligand, which can positively influence the course of CPHD due to COPD through reduction of apoptosis of alveolar cells and cardiomyocytes.

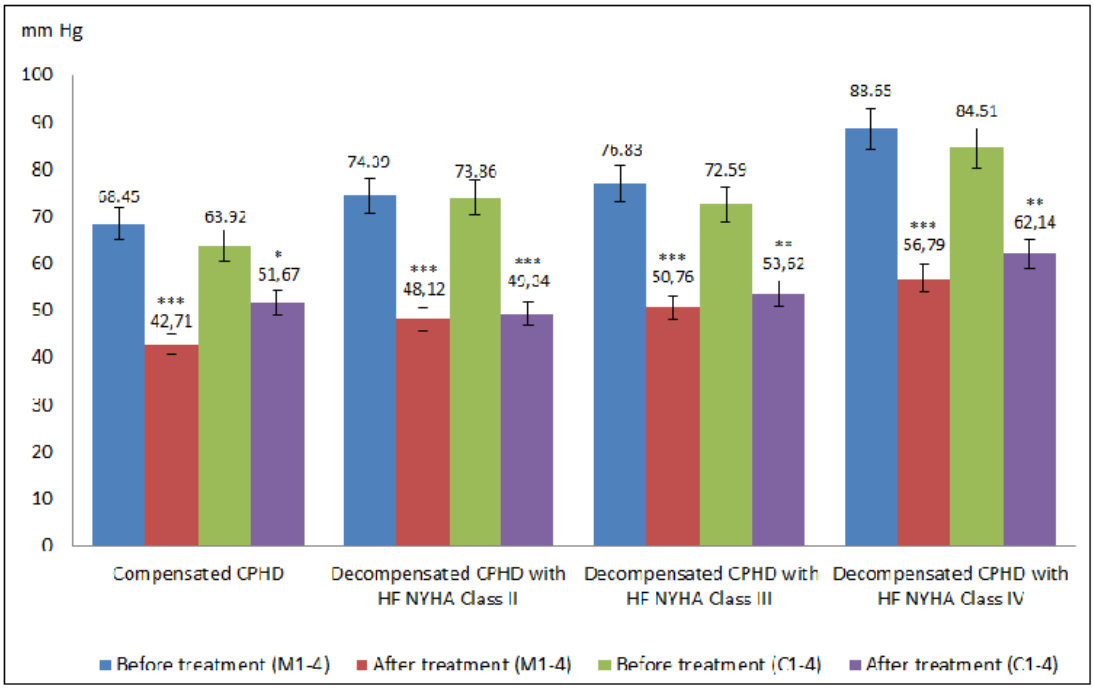
Interesting results were obtained during the analysis of the dynamics of the studied values using the principle "the main subgroups vs. control subgroups" with the use of Fisher's exact test (pF). It was marked that in the case of compensated CPHD the complex pharmacotherapy with the angiotensin II receptor blocker candesartan was more effective than just BT with reference to bFGF ($pF = 0.047$), VEGF ($pF = 0.026$), and FasL ($pF = 0.036$).

In patients with decompensated CPHD with CHF NYHA Class II the use of candesartan on the background of the basic therapy was associated with significant changes of the bFGF level ($pF = 0.038$), but in relation to VEGF and FasL no better effect was seen in comparison with ACE inhibitor enalapril (or $pF = 0.064$; $pF = 0.391$).

A positive dynamics of VEGF (respectively $pF = 0.042$; $pF = 0.045$) was observed in the cases of

decompensated CPHD with CHF NYHA Class III - IV during the combined use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on the background of BT; it remained pronounced with reference to apoptosis inducer Fas -Ligand in the cases of CPHD with CHF NYHA Class III (pF = 0.023), but became less reliable in the cases of CHF NYHA Class IV (pF = 0.094).

Lowering of the bFGF and VEGF levels in blood was accompanied by a reduction of PAH (Fig. 1). The dynamics of the PASP value has proved this. Thus, in patients of the main subgroup with compensated CPHD the 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. The PASP level decreased from (74.39 ± 5.26) mm Hg to (48.12 ± 4.53) mm Hg, so by an average of 35,3% ($p < 0.001$), in patients of the main subgroup with decompensated CPHD with CHF NYHA Class II; while in the control subgroup this level decreased from (73.86 ± 4.97) mm Hg to (49.34 ± 3.91) mm Hg, by an average of 33,2% ($p < 0.001$).



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 PASP levels under the influence of various versions of pharmacotherapy in patients with CPHD.

Thus, the effect of the PASP level reduction under the influence of ACE inhibitor enalapril or the angiotensin II receptor blocker candesartan did not differ statistically in both groups ($p > 0.05$).

More pronounced PASP dynamics was in patients with decompensated CPHD with CHF 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 (50.76 ± 4,23) mm Hg, which comprised an average of 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% ($p < 0.01$).

At the same time, the PASP level decreased from (88.65 ± 6.74) mm Hg to (56.79 ± 5.12) mm Hg,by an average of 35,9% ($p < 0.001$) in the patients of the main subgroup with decompensated CPHD with CHF NYHA Class IV; while in the control subgroup it decreased from (84.51 ± 5.29) mm Hg to (62.14 ± 4.80) mm Hg, by an average of 26,5% ($p < 0.01$).

Taking into account the role of the elevated bFGF and VEGF levels in the pathogenesis of PAH in patients with COPD[2,6,7], this effect can have a positive impact on the development and progression of right ventricular CHF 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 to 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 levels of bFGF, VEGF, FasL and PASP 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 [9].Also, the results on the positive effect of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan on levels of bFGF, VEGF, FasL, PASP 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[15].

The development of side effects of the studied drugs was not noticed during the period of treatment; these medications were well tolerated by the patients and combined well with the standard basic therapy.

4. Conclusions

1. ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan with lower levels of mitogenic growth factors bFGF, VEGF, apoptosis inducer Fas-Ligand, and PASP in patients with CPHD.
2. Clinical efficacy of long-term (over 6 months) 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 CHF NYHA Class III - IV taking into account the dynamics of the levels of bFGF, VEGF, FasL, and PASP was more pronounced, than after the same treatment but without the angiotensin II receptor blocker.
3. The use of ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan in patients with compensated and decompensated CPHD is safe and appropriate for 6-month courses of use.

4.1 Prospects for Further Research in this Direction are the study of the levels of mitogenic growth factors bFGF, VEGF, apoptosis inducer Fas-Ligand, and PASP in conjunction with the values of cardiac hemodynamics in patients with CPHD.

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