THE DYNAMICS OF SERUM LEVELS OF THE ANGIOGENIC CYTOKINES AND APOPTOSIS INDUCERS UNDER THE INFLUENCE OF INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN PATIENTS WITH CHRONIC PULMONARY HEART DISEASE

V. Seredyuk
Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Abstract. The dynamics of serum levels of the angiogenic cytokines was investigated, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and apoptosis inducer Fas-Ligand (FasL) 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 and chronic heart failure (CHF) NYHA Class II-IV. 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 levels is more pronounced, than during the same treatment but without the angiotensin II receptor blocker.

Key words: chronic pulmonary heart disease, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, basic fibroblast growth factor, vascular endothelial growth factor, apoptosis inducer Fas-ligand

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.

The aim of this study was to assess the dynamics of the serum levels of the angiogenic cytokines bFGF, VEGF, and apoptosis inducer Fas-Ligand 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.
Material 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 2016) [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 (M₁) – 29 patients with compensated CPHD that were treated according to the scheme: basic therapy + candesartan (BT + C); the second (M₂) – 36 patients with decompensated CPHD and CHF NYHA Class II, which also received candesartan in addition to the basic treatment (BT + C); the third (M₃) subgroup – 39 patients with decompensated CPHD and CHF NYHA Class II, in which on the background of the basic therapy enalapril and the angiotensin II receptor blocker candesartan (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. 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 at the beginning of the research and after 6 months of the treatment.

All analyses were undertaken using the Statistica 12.0 (StatSoft, Tulsa, OK, USA). Statistical significance was assumed at p<0.05.

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.

The analysis of the dynamics of VEGF (Tab. 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 31.18% (p <0.01), and in the control subgroup – from (376.94 ± 18.56) pg / ml to (245.15 ± 17.32) pg / ml, by an average of 34.96% (p < 0.01).

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 (Tab. 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).

FasL 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 NYHA Class 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 (194.38 ± 29.61) 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 23.45% (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 re-
duce 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.

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.

Received data on more severe clinical effectiveness and positive impact on levels of bFGF, VEGF, FasL 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, 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].

Conclusion

1. ACE inhibitor enalapril and the angiotensin II receptor blocker candesartan with lower levels of the angiogenic cytokines bFGF, VEGF, and apoptosis inducer Fas-Ligand 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, and FasL 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.

Prospects for further research in this direction are the study of the levels of mitogenic growth factors bFGF, VEGF, and apoptosis inducer Fas-Ligand in conjunction with the values of cardiac hemodynamics in patients with CPHD.

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The dynamics of serum levels of the angiogenic cytokines bFGF, VEGF, and apoptosis inducer FasL in patients with CPHD

Table 1. The influence of ACE inhibitor enalapril, the angiotensin II receptor blocker candesartan, and their combined use on the dynamics of the serum levels of the angiogenic cytokines bFGF, VEGF, and apoptosis inducer FasL in patients with CPHD

<table>
<thead>
<tr>
<th>Groups</th>
<th>bFGF, pg/ml</th>
<th>VEGF, pg/ml</th>
<th>FasL, pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The main group</td>
<td>The control group</td>
<td>The main group</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
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<tr>
<td>Compensated CPHD (M1 – n=29 vs C1 – n=26)</td>
<td>37.62± 4.36</td>
<td>22.81± 3.92***</td>
<td>32.54± 5.01</td>
</tr>
<tr>
<td>Decompensated CPHD with CHF NYHA Class II (M2 – n=36 vs C2 – n=33)</td>
<td>51.16± 5.24</td>
<td>36.57± 4.95*</td>
<td>44.37± 4.38</td>
</tr>
<tr>
<td>Decompensated CPHD with CHF NYHA Class III (M3 – n=39 vs C3 – n=35)</td>
<td>58.12± 7.83</td>
<td>53.68± 8.61***</td>
<td>42.71± 7.34</td>
</tr>
<tr>
<td>Decompensated CPHD with CHF NYHA Class IV (M4 – n=43 vs C4 – n=41)</td>
<td>66.72± 8.24</td>
<td>60.57± 7.53</td>
<td>49.35± 8.93</td>
</tr>
</tbody>
</table>

Note: 1. M1-4 – the subgroups of the main group; 2. C1-4 – the subgroups of the control group; 3. p – the reliability coefficient:*p<0.05;**p<0.01;***p<0.001.


Corresponding author:
Vitaliy Seredyuk, MD, DMedSc, PhD, Professor of Internal Medicine №2 and Nursing department of Ivano-Frankivsk National Medical University, Ukraine vitaliyvseredyuk@gmail.com