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# Role of Aldosterone, Mitogenic Growth Factors, Apoptosis Inducers and Pulmonary Arterial Hypertension in the Formation and Progression of Chronic Pulmonary Heart Disease

Vitaliy Serebyuk <sup>1\*</sup>

1. Department of Internal Medicine № 2, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine  
[E-mail: [vseredyuk@inbox.ru](mailto:vseredyuk@inbox.ru); Tel: +38-0992339110]

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We have investigated the role of mineralocorticoid aldosterone, mitogenic growth factors – fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), apoptosis inducer Fas-Ligand (FasL) and pulmonary arterial hypertension (PAH) in the formation and progression of chronic pulmonary heart disease (CPHD). I was found that increased levels of aldosterone, mitogenic growth factors bFGF and VEGF, apoptosis inducer FasL and PAH were observed in cases of decompensated CPHD with development and progression of chronic heart failure.

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**Keyword:** Chronic Pulmonary Heart Disease, Pulmonary Arterial Hypertension, Aldosterone, Fibroblast Growth Factor, Vascular Endothelial Growth Factor, Apoptosis Inducer.

### 1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) remains a major public health problem. In 2020, COPD is projected to rank fifth worldwide in burden of disease, according to a study published by the World Bank/World Health Organization<sup>[7]</sup>. Chronic pulmonary heart disease (CPHD) is one of the severe complications of COPD and is characterized by high mortality<sup>[5]</sup>.

According to the data of numerous studies, pulmonary arterial hypertension (PAH) is the major pathological mechanism of CPHD formation<sup>[11,15]</sup>.

On the other hand, mitogenic growth factors can be actively involved in the development and progression of CPHD. In particular, in patients with CPHD due to COPD, there is a significant increase of basic fibroblast growth factor level

(bFGF) in urine and blood plasma<sup>[3]</sup>, which can cause the proliferation of endothelial and vascular smooth muscle cells of the pulmonary circulation<sup>[9]</sup>.

At the same time, another mitogenic factor – vascular endothelial growth factor (VEGF) and its receptors are involved in the development of abnormal pulmonary vascular remodeling in patients with COPD<sup>[8]</sup>. Moreover, there is a synergism observed between the expression of bFGF and VEGF on the one hand; the induction of angiogenesis and microvessel on the other hand<sup>[13]</sup>.

Activation of apoptotic cells is also important for the development of CPHD. There are evidences that in case of CPHD due to COPD the activation of cardiomyocytes apoptosis<sup>[4]</sup> and alveolar cells<sup>[1]</sup> takes place, which contributes to the

progression of CPHD<sup>[11]</sup>. Apoptosis inducer Fas-Ligand (FasL) serves as the marker of this process<sup>[12]</sup>.

Recently, new data on the role of the renin-angiotensin-aldosterone system (RAAS), and pulmonary vascular endothelium in the formation of PAH and the pathogenesis of CPHD have appeared<sup>[2,6]</sup>.

The above mentioned mechanisms lead to the remodeling of the right heart and the progression of chronic heart failure (CHF) in these patients<sup>[5,11,14]</sup>.

### 1.1 The Aim of Research

Examine the role of mineralocorticoid aldosterone, as the element of RAAS, mitogenic growth factors bFGF and VEGF, apoptosis inducer Fas-Ligand and pulmonary arterial hypertension in the formation and progression of chronic pulmonary heart disease.

### 2. Materials and Methods

282 patients with CPHD due to COPD Stage II-IV were examined, including 55 (19.5%) with compensated and 227 (80.5%) with decompensated CPHD. Among the surveyed patients 214 (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)<sup>[7]</sup>, and CPHD – on the basis of the WHO criteria<sup>[14]</sup>.

The diagnosis and the stage of heart failure were established based on the Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology<sup>[10]</sup>.

The patients were divided into the following groups: 1-55 patients with compensated CPHD; 2-69 patients with decompensated CPHD and CHF NYHA Class II; 3-74 patients with decompensated CPHD and CHF NYHA Class III; and 4-84 patients with decompensated CPHD with CHF NYHA Class IV.

Determination of aldosterone levels (“DSL”, USA), bFGF (“Biosource”, USA), VEGF (“Cytimmune”, USA), and FasL (“Diaclone”, USA) was performed using the immunoenzyme method.

The indices of 27 healthy individuals, at (28.4±2.9) years of age, served as criterion standard for determination of the reference rate of aldosterone, bFGF, VEGF, and FasL.

Doppler determination of pulmonary artery systolic pressure (PASP) was performed to assess the dynamics of PAH by a standard method.

A statistical processing of the results was performed with the help of software packages Statistica v 8.0 (“Stat Soft”, USA).

### 3. Results and Discussion

We began the analysis of the results with an assessment of serum levels of aldosterone; mitogenic growth factors bFGF, VEGF; and apoptosis inducer Fas-Ligand with different types of CPHD course- compensated and decompensated CHF NYHA Class II-IV (Table 1).

Aldosterone level in the examined patients was considerably higher than the normal values of this important neurohumoral RAAS factor. It was established that at the stage of compensation, CPHD is characterized by a significant increase in the blood level of aldosterone to (111.62±10.74) pg / ml vs. (56.85±6.91) pg / ml in healthy individuals ( $p < 0.05$ ). In the case of CPHD decompensation with the development of CHF NYHA Class II aldosterone level naturally increases, rising to (141.66±12.83) pg / ml ( $p < 0.01$ ); and in the case of progression of CPHD decompensation NYHA Class III – up to (197.94±18.32) pg / ml ( $p < 0.001$ ). The most pronounced increase of the level of circulating aldosterone was found in critically ill patients with CPHD with CHF NYHA Class IV, in which this level reached (231.56±22.40) pg / ml and was over the limit by a factor of 4.1 times ( $p < 0.001$ ).

These results are consistent with the data on an increase in aldosterone production due to activation of RAAS in patients with CPHD with CHF<sup>[2,6]</sup>.

During the analysis was found that the level of bFGF increases as well as the one in healthy individuals on the early stages of CPHD development – in cases of compensated CPHD and decompensated CPHD with CHF NYHA Class II. Thus, in the presence of compensated CPHD the level of bFGF serum was  $(35.47 \pm 5.84)$  pg / ml, in patients with decompensated CPHD with CHF NYHA Class II –  $(48.29 \pm 6.73)$  pg / ml, which exceeded, respectively, by 53.2% and 61.5% , the value of this index in healthy individuals  $(18.61 \pm 4.96)$  pg / ml ( $p < 0.01$ ). High levels of concentration of bFGF serum reached in patients with decompensated CPHD with CHF NYHA Class III –  $(55.36 \pm 9.20)$  pg / ml, and with CHF NYHA Class IV –  $(63.48 \pm 8.65)$  pg / ml, that is, respectively, by 66.4% and 70.7%, as compared with healthy individuals ( $p < 0.001$ ). Moreover, excess of bFGF levels by an average of 36.1% was observed in patients with decompensated CPHD with CHF NYHA Class II, as compared with the patients with compensated CPHD ( $p < 0.01$ ). It was also found that, in comparison with CPHD with CHF NYHA Class II, serum level of bFGF in patients with NYHA Class III was higher by 15.2% ( $p < 0.05$ ), and case of CHF NYHA Class IV, compared with CHF NYHA Class III – by 13.9% ( $p < 0.05$ ).

Our results are consonant with the data on the relationship between excessive production of bFGF serum, which leads to a pronounced induction of neoangiogenesis and interstitial fibrosis heart in the case of CPHD due to COPD<sup>[3,5,9]</sup>. On the other hand, considering the data on the ability of angiotensin-II to activate the synthesis of bFGF with cardiac fibroblasts<sup>[4]</sup>, we can explain the obtained results by comparing the dynamics of aldosterone levels, depending on the stage of CPHD.

Analysis of the VEGF levels allowed us to state, that at the time of CPHD compensation takes place a significant increase of its content to  $(19.79 \pm 3.82)$  pg / ml, in comparison to the reference value  $(7.95 \pm 1.38)$  pg / ml, so by an average of 59.8% ( $p < 0.05$ ). Further increase of the VEGF level to  $(21.46 \pm 3.24)$  pg / ml, so by an average of 62.9% compared to its normal level ( $p < 0.01$ ), was noticed in the case of CPHD

decompensation with slight CHF NYHA Class II. The most significant increase of VEGF concentration in blood in the examined patients was noticed with CPHD decompensation with CHF NYHA Class III, in which it reached  $(32.35 \pm 2.87)$  pg / ml vs. the reference value of  $(7.95 \pm 1.38)$  pg / ml, so by 75.4% ( $p < 0.001$ ). On the other hand, in patients with CPHD with severe CHF NYHA Class IV there was less significant, in relation to CHF NYHA Class III, increased concentration of VEGF in blood - to  $(22.63 \pm 2.79)$  pg / ml vs.  $(7.95 \pm 1.38)$  pg / ml in healthy individuals (by an average of 64.8%;  $p < 0.01$ ). In this case, the increase of the VEGF level in patients with decompensated CPHD with CHF NYHA Class III, relatively to its level in the case of compensated CHF, comprised an average of 38.8% ( $p < 0.01$ ), relatively to CHF NYHA Class II – 33.7% ( $p < 0.05$ ), and relatively to severe CHF NYHA Class IV – 30.1% ( $p < 0.05$ ). At the same time, a tendency to the VEGF level increase was observed in the case of CHF NYHA Class IV, in reference to compensated CPHD, by 12.5% ( $p > 0.05$ ).

Thus, addition of CHF to CPHD fundamentally affects the growth of VEGF. Such dynamics is less pronounced in the case of CPHD without signs of CHF.

Such activation of a synthesis factor of development and progression of VEGF endothelial dysfunction in patients with COPD was noted in several other studies<sup>[8]</sup>.

In addition, activation of apoptosis was observed in all patients with CPHD. Its intensity increased with the transition of CPHD from the compensation phase to the decompensation phase, as well as with the progression of CPHD.

Thus, the most intense activation of apoptosis was observed in the patients with decompensated CPHD with CHF NYHA Class III, in which the FasL level in relation to its reference value  $(115.91 \pm 12.32)$  pg/ml, increased to  $(382.64 \pm 35.93)$  pg / ml ( $p < 0.001$ ). An increase in the concentration of FasL to  $(265.86 \pm 23.40)$  pg / ml vs.  $(115.91 \pm 12.32)$  pg / ml normally ( $p < 0.01$ ) was noticed in patients with compensated CPHD. The growing value of FasL serum comprised an average of 69.7% in the case of CPHD with CHF

NYHA Class III; and 56.4% in the case of compensated CPHD relatively to the healthy individuals (respectively  $p < 0.001$  and  $p < 0.01$ ). An increase in blood level of FasL to  $(314.55 \pm 29.73)$ , relatively to the reference value  $(115.91 \pm 12.32)$  pg / ml, so was up by 63.1% ( $p < 0.001$ ), was observed in the case of

decompensated CPHD with CHF NYHA Class II. In the case severe CPHD decompensation with CHF NYHA Class IV apoptosis intensity did not progress, and the value of FasL reached  $(273.24 \pm 27.65)$  pg / ml vs.  $(115.91 \pm 12.32)$  pg / ml in healthy individuals, which comprised 57.6% ( $p < 0.01$ )

**Table 1:** Blood levels of aldosterone, mitogenic growth factors bFGF and VEGF, apoptosis inducer FasL in patients with CPHD.

Groups	Aldosterone, pg/ml	bFGF, pg/ml	VEGF, pg/ml	FasL, pg/ml
Healthy individuals (n=27)	56.85±6.91	18.61±4.96	7.95±1.38	115.91±12.32
Compensated CPHD (n=55)	111.62±10.74	35.47±5.84**	19.79±3.82*	265.86±23.40**
Decompensated CPHD with CHF NYHA Class II (n=69)	141.66±12.83**	48.29±6.73**	21.46±3.24**	314.55±29.73***
Decompensated CPHD with CHF NYHA Class III (n=74)	197.94±18.32***	55.36±9.20***	32.35±2.87***	382.64±35.93***
Decompensated CPHD with CHF NYHA Class IV (n=84)	231.56±22.40***	63.48±8.65***	22.63±2.79**	273.24±27.65**

Note: p – the reliability coefficient against the reference norm: \* –  $p < 0.05$ ; \*\* –  $p < 0.01$ ; \*\*\* –  $p < 0.001$ .

The received results prove the activation of apoptosis, the marker of which is the inducer Fas-Ligand<sup>[12]</sup>, in patients with CPHD due to the different stages of COPD.

Characteristically, that in patients with decompensated CPHD with severe CHF was noted a more severe COPD course with the prevalence of Stage III and IV, whereas in the patients with compensated CPHD and slightly expressed CHF NYHA Class II was mostly COPD Stage II. In particular, 51 (91.7%) patients with compensated CPHD had COPD Stage II, COPD Stage II and only 4 (7.3%) – Stage III. At the same time, only in 52 (75.4%) patients was observed COPD Stage II in the case of CPHD with CHF NYHA Class II, and COPD Stage III – in 17 (24.6%) patients. In 54 (72.9%) patients with severe CHF NYHA Class III was stated COPD Stage III, while in 20 (27.1%) was stated COPD Stage IV. COPD Stage IV was stated in the vast majority, so in 78 (92.8%) patients, that belonged to the group of patients with the most severe CHF NYHA Class IV had, and COPD Stage III was verified only in 6 (7.2%) patients from this group.

Thus, the stage of COPD may affect the level of aldosterone mitogenic growth factors bFGF, VEGF, and apoptosis activation. A significant increase in the levels of aldosterone, mitogenic growth factors bFGF and VEGF, apoptosis FasL was observed with the development of decompensated CPHD and progression of heart failure.

Also found that with the development of decompensation CPHD with CHF was observed the progression of PAH. Thus, in patients with compensated CPHD level of PASP was  $(65.37 \pm 3.82)$  mmHg, patients with decompensated CPHD with CHF NYHA Class II –  $(74,61 \pm 5,49)$  mmHg, patients with decompensated CPHD with CHF NYHA Class III –  $(75,83 \pm 5,26)$  mmHg, and in patients with decompensated CPHD with CHF NYHA Class IV –  $(87,42 \pm 6,15)$  mmHg.

As is known, pulmonary arterial hypertension is defined as a PASP of  $> 35$  mmHg at rest<sup>[11]</sup>.

The results of the study suggest a role for increasing the level of aldosterone, bFGF, VEGF and FasL in the formation and progression of PAH in patients with CPHD.



#### 4. Conclusions

1. In the patients with CPHD production of aldosterone is activated in the case of compensated CPHD and amplified in the case of decompensated CPHD, increasing with the progression of CHF from NYHA Class II to NYHA Class IV.
2. In the patients with CPHD at the early stages of formation the synthesis of mitogenic growth factors bFGF, and VEGF is enhanced; which reaches the maximum level during the development of CHF NYHA Class III (VEGF) and CHF NYHA Class IV (bFGF).
3. The intensity of the level of apoptosis according to the FasL marker in the examined patients progresses with the development of CPHD decompensation from CHF NYHA Class II to CHF NYHA Class III, and in the case of severe CHF NYHA Class IV further increase the FasL level does not occur.
4. The increased levels of aldosterone, bFGF, VEGF and FasL leads to the formation and progression PAH in patients with CPHD.

#### 4.1 Prospects for Further Research in this

**Direction:** are to study the dynamics of aldosterone, mitogenic growth factors and apoptosis inducer in relation to the indices of cardiac hemodynamics in patients with CPHD.

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