



The Egyptian Society of Chest Diseases and Tuberculosis  
**Egyptian Journal of Chest Diseases and Tuberculosis**

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## Evaluation of erythropoietin hormone in chronic obstructive pulmonary disease patients during exacerbation and after remission

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Received 26 July 2016; accepted 30 August 2016

**Abstract Introduction:** It has long been known that COPD causes polycythemia secondary to erythrocytosis caused by hypoxia present in advanced cases of COPD. However, it was shown in several studies that some COPD patients had anemia rather than erythrocytosis

**Aim:** The aim of this work was to assess the changes in erythropoietin in COPD patients during exacerbation and after remission.

**Subjects and methods:** This work was done on 50 subjects, Group I: 40 COPD patients plus Group II: 10 age matched apparently healthy control subjects. For all history taking, full clinical exam, PFTs (spirometry), EPO hormone measurement on human serum by ELIZA (EPO hormone was measured during exacerbation and after remission), oxygen saturation and routine labs (CBC, Liver and Renal function) were performed.

**Results:** Level of erythropoietin hormone was significantly higher in COPD patients with mean ( $21.92 \pm 6.64$  mU/ml) than control with mean ( $9.42 \pm 1.5$  mU/ml) and higher during remission ( $24.21 \pm 6.58$  mU/ml) than during exacerbation ( $21.92 \pm 6.64$  mU/ml), also was significantly higher during remission in grade (II, III) ( $25.68 \pm 2.57$ ,  $33.71 \pm 2.16$  mU/ml) than grade (I, IV) ( $16.04 \pm 0.89$ ,  $19.39 \pm 1.28$  mU/ml) COPD patients respectively. Erythropoietin hormone level was significantly higher in anemic than non anemic COPD patients. It was ( $27.94 \pm 6.33$  mU/ml) ( $20.84 \pm 4.83$  mU/ml) respectively, and it was significantly inversely related to oxygen saturation & both of HB and Hct in COPD patients.

**Conclusion:** EPO hormone level was significantly higher in grade (II, III) than grade (I, IV) COPD patients ( $p = 0.005$ ), and also COPD with anemia was higher in stage (II, III) than stage (I, IV), EPO hormone level significantly higher in anemic than non anemic COPD

**Abbreviations:** Hct, hematocrit; HB, hemoglobin; EPO, erythropoietin hormone.

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

<http://dx.doi.org/10.1016/j.ejcdt.2016.08.015>

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Please cite this article in press as: A.G. El Gazzar et al., Evaluation of erythropoietin hormone in chronic obstructive pulmonary disease patients during exacerbation and after remission, Egypt. J. Chest Dis. Tuberc. (2016), <http://dx.doi.org/10.1016/j.ejcdt.2016.08.015>

patients and was significantly higher ( $p = 0.005$ ) during remission than during exacerbation.

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## Introduction

COPD is a common preventable and treatable disease, characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1]. Acute exacerbation of chronic obstructive pulmonary disease is defined as acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medications [1]. Erythropoietin is an endogenous glycoprotein hormone that controls erythropoiesis, or red blood cell production. It is a cytokine (protein signaling molecule) for erythrocyte (red blood cell) precursors in the bone marrow. Human EPO has a molecular weight of 34 kDa also called hematopoietin or hemopoietin [2]. Diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase [3]. It has long been known that COPD causes polycythemia secondary to erythrocytosis caused by hypoxia present in advanced cases of COPD [4]. However, it was shown in several studies that some COPD patients had anemia rather than erythrocytosis [5].

## Aim of the work

This work was carried out to assess the changes in erythropoietin in COPD patients during exacerbation and after remission.

## Subjects and methods

This study was performed in Banha University Hospitals Chest Department on 50 subjects during December 2014 and December 2015. They were divided into 2 groups: *Group 1*: 40 patients with COPD, Erythropoietin (EPO) hormone will be measured during exacerbation and after remission. *Group 2*: 10 apparently healthy subjects.

### Inclusion criteria

Patients with COPD diagnosed according to GOLD [1] criteria.

### Exclusion criteria

Patients with history of bronchial asthma, malignancy, haematologic disorder, systematic or autoimmune disorder, thyroid disease, liver cirrhosis, heart failure, gastrointestinal or other hemorrhage, renal failure and history of blood transfusion in the last 4 months were included.

All subjects were submitted to the following:

- (1) *History taking*: History of smoking, chest symptoms and any other co-morbidities.
- (2) *Clinical examination*: Both general and local examination.
- (3) *Radiological examination*: Plain chest X ray postero-anterior and left lateral views.
- (4) *Pulmonary function tests (spirometry)* before and after bronchodilatation.
- (5) *Routine investigations as*: Electrocardiography, complete blood count, liver function tests, kidney function tests and blood sugar testing.
- (6) *Measuring the oxygen saturation* in the blood by pulse oximetry.
- (7) *Erythropoietin hormone measurement*:

–The determination of EPO should be performed on human serum by ELISA.

Three cm of whole blood without adding any anticoagulant was collected in the morning between 7:30 a.m. to 12:00 noon, because diurnal variation of erythropoietin has been reported [6]. Allow blood to clot between 2 and 8 °C. Then, the serum should be promptly separated, preferably in a refrigerated centrifuge, and stored at –15 °C or lower. Serum samples frozen at –15 °C are stable for up to 12 month.

–*Range of EPO in healthy individuals*: (0–19) mU/ml (milliunits per milliliter [7]).

## Results

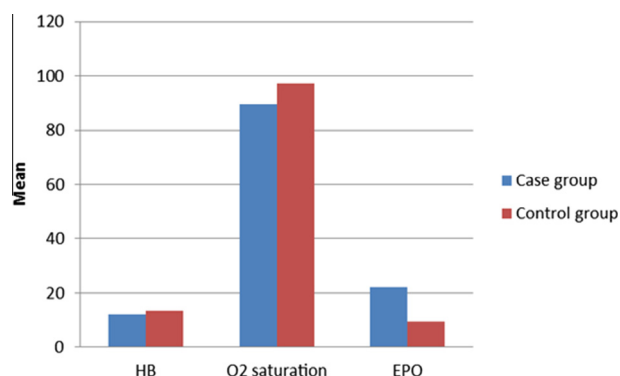
Table 1 shows that: (82.5%) were males and (17.5%) were females COPD patients. The mean age for patients was

**Table 1** Demographic data of studied group.

	Case group	Control group
<i>Sex n&amp;%</i>		
Male	33 (82.5%)	5 (50%)
Female	7 (17.5%)	5 (50%)
<i>Age in years</i>		
Range	47–61	46–61
Mean ± SD	54.88 ± 7.48	53.0 ± 6.57
<i>FVC %</i>		
Range	30–71	47–75
Mean ± SD	48.2 ± 11.94	61.1 ± 14.18
<i>FEV1 %</i>		
Range	17–81	47–79
Mean ± SD	39.9 ± 18.17	63.7 ± 16.84
<i>FEV1/FVC %</i>		
Range	26–69	80–101
Mean ± SD	54.25 ± 12.83	90.5 ± 10.75

**Table 2** Comparison of erythropoietin, oxygen saturation and hemoglobin between case and control groups.

	Case group (mean $\pm$ SD)	Control group (mean $\pm$ SD)	St <i>t</i> test	<i>p</i> value
<i>Sex n&amp;%</i>				
Male	33(82.5%)	5(50%)	3.02	
Female	7(17.5%)	5(50%)		
Age in years	54.88 $\pm$ 7.48	53.0 $\pm$ 6.57	0.725	> 0.05
HBgm/dl	11.96 $\pm$ 1.69	13.25 $\pm$ 0.63	2.35	< 0.05
O <sub>2</sub> saturation %	89.63 $\pm$ 2.88	97.4 $\pm$ 0.52	8.44	< 0.005
EPO mU/ml	21.92 $\pm$ 6.64	9.42 $\pm$ 1.5	5.87	< 0.005

**Figure 1** Comparison of erythropoietin, oxygen saturation and hemoglobin between case and control groups.

54.88  $\pm$  7.48 years and for control was 53.0  $\pm$  6.57. FEV1% and FVC% were significantly higher in control group than in case group.

Table 2 and Fig. 1 show that hemoglobin and Oxygen saturation were significantly lower in cases than in control groups, and EPO level was significantly higher in cases than in control groups.

Table 3 and Fig. 2 show that EPO hormone level was significantly higher in grade (II, III) than grade (I, IV) COPD patients and that it is higher during remission than during exacerbation of COPD.

Table 4 shows that COPD with anemia was higher in stage (II,III) than stage (I,IV). EPO hormone level was significantly

higher in anemic than non anemic COPD patients during remission and exacerbation

Table 5 shows that EPO hormone level was significantly higher during remission than during exacerbation and Oxygen saturation was significantly higher during remission than during exacerbation.

Table 6 and Fig. 3 show a significant negative correlation between EPO hormone level and both HB & Hct level in COPD patients.

Table 7 shows a significant negative correlation between EPO hormone level and Oxygen saturation during exacerbation and remission in COPD patients.

## Discussion

The study was aiming at assessment of erythropoietin changes in different stages of COPD as COPD is traditionally associated with polycythemia (5) also the assumption that anemia frequently occurs in patients with COPD (8). This study was conducted on 50 subjects, 40 COPD patients 33 males (82.5%) and 7 females (17.5%) (EPO hormone will be measured during exacerbation and after remission) their age ranging from 47 to 61 years plus 10 age matched apparently healthy control group 5 males (50%) and 5 females (50%) their age ranging from (46 to 61) years and that both FEV1%, FVC % were significantly higher in the control group than in the case group (Table 1).

In the current study, the level of EPO hormone was found to be higher in COPD patients with mean (21.92  $\pm$  6.64 mU/ml) compared to controls with mean (9.42  $\pm$  1.5 mU/ml)

**Table 3** Comparison of erythropoietin hormone level in COPD patients gradings.

Grades	Grade I	Grade II	Grade III	Grade IV	<i>F</i> test	<i>p</i> value
EPO mU/ml during acute exacerbation	13.91 $\pm$ 0.65	23.49 $\pm$ 2.6	31.53 $\pm$ 1.98	16.94 $\pm$ 1.23	159.74	< 0.005
EPO mU/ml during remission	16.04 $\pm$ 0.89	25.68 $\pm$ 2.57	33.71 $\pm$ 2.16	19.39 $\pm$ 1.28	145.6	< 0.005

**Table 4** Comparison between EPO hormone and COPD grading in COPD patients with and without anemia.

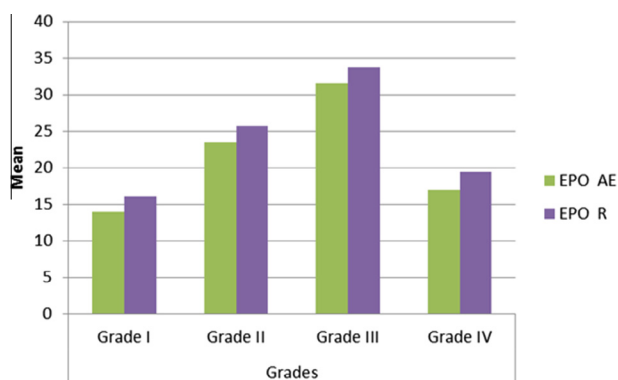
	Case group with anemia (19) mean $\pm$ SD	Case group without anemia (21) mean $\pm$ SD	St test	<i>p</i> value
EPO mU/ml AE	25.64 $\pm$ 6.28	18.55 $\pm$ 5.05	3.95	< 0.005
EPO mU/ml R	27.94 $\pm$ 6.33	20.84 $\pm$ 4.83	4.01	< 0.005
<i>Grade n &amp; %</i>				
Stage I: Mild	0(0.0)	4(19.0%)		
Stage II: Moderate	7(36.8%)	3(14.3%)	12.58	< 0.005
Stage III Severe	8(42.1%)	2(9.5%)		
Stage IV: Very severe	4(21.1%)	12(57.1%)		

**Table 5** Comparison of O<sub>2</sub> saturation and EPO during exacerbation and after remission in COPD patients.

Among cases (40)	During exacerbation (mean ± SD)	After remission (mean ± SD)	Paired <i>t</i> test	<i>p</i> value
O <sub>2</sub> saturation %	89.63 ± 2.88	92.53 ± .24	12.38	< 0.005
EPO mU/ml	21.92 ± 6.64	24.21 ± 6.58	16.13	< 0.005

**Table 6** Correlation between EPO hormone level and both Hemoglobin and Hct levels in groups of COPD patients.

Among COPD patients	EPO	
	<i>R</i>	<i>p</i>
HBgm/dl	-0.492	< 0.005
Hct %	-0.516	< 0.005

**Figure 2** Comparison of Erythropoietin hormone level in COPD patients gradings.

and the difference between them was statistically highly significant ( $p < 0.005$ ) (Table 2 and Fig. 1).

In the current study, the concentration of hemoglobin was lower in COPD cases with mean ( $11.96 \pm 1.69$  g/dl) compared to controls hemoglobin mean ( $13.25 \pm 0.63$  g/dl) and the difference between them was statistically significant ( $p < 0.05$ ) (Table 2 and Fig. 1).

Oxygen saturation in COPD patients was lower than controls and its mean in COPD patients was ( $89.63 \pm 2.88\%$ ) while for control was ( $97.4 \pm 0.52\%$ ) and the difference between them was statistically highly significant ( $p < 0.005$ ) (Table 2 and Fig. 1).

These results agree with [9] who measured the level of hemoglobin, hematocrit, oxygen saturation in blood and erythropoietin hormone in (41) patients with COPD and ten healthy age and sex matched control subjects and the results showed that mean hemoglobin for COPD cases was ( $13.82 \pm 1.95$  g/dL) while for the control it was ( $14 \pm 1.27$  g/dl) with no statistical significance. Mean value of Hematocrit was ( $42.1 \pm 6.09\%$ ) for COPD and ( $43.8 \pm 3.19\%$ ) for control and result was not statistically significant. However oxygenation parameters in ABGs showed statistically significant differences between the COPD patients and the control group SaO<sub>2</sub> was ( $84.9 \pm 14.7$ ) and ( $96.80 \pm 1.40$ ) for COPD cases and control respectively.

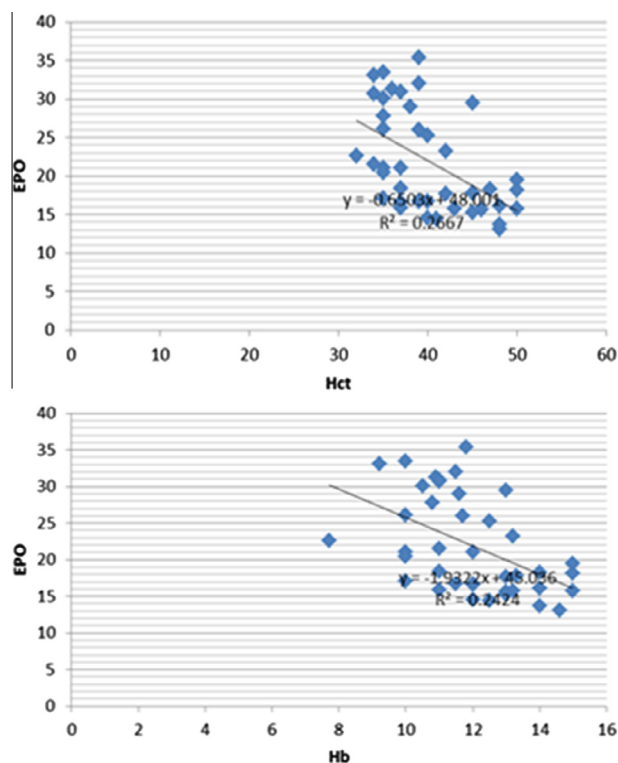
The results of this study also were in agreement with [5] who found that EPO serum level was higher in COPD patients

than in control groups. In the current study, COPD patients were divided into 4 stages according to (1) and erythropoietin was correlated to degree of severity of COPD in (Tables 3 and 4 and Fig. 2), the results found that EPO hormone level was higher during remission than exacerbation of COPD patients and difference was statistically highly significant ( $p < 0.005$ ). It was found that EPO hormone levels during remission were low in stage I disease ( $16.04 \pm 0.89$  mU/ml), increased in stage II ( $25.68 \pm 2.57$  mU/ml), while maximally increased in stage III ( $33.71 \pm 2.16$  mU/ml) and then decreased in stage IV ( $19.39 \pm 1.28$  mU/ml). On reflecting these changes on the routinely measured parameters of complete blood picture, the percentage of anemia in stage I disease was (0%) and increased to (36.8%) in stage II, reaching (42.1%) in stage III dropping again to (21.1%) in stage IV.

These results are in agreement with [9] who found that the erythropoietin hormone level was ( $15.24 \pm 2.6$  mU/ml) in stage I disease, ( $22.61 \pm 5.68$  mU/ml) in stage II, ( $33.59 \pm 4$  mU/ml) in stage III, then decrease to ( $17.9 \pm 3.3$  mU/ml) in stage IV. Also the total percentage of anemia in COPD patients was (46.3%), in comparison to (51.3%) non anemic and (2.4%) polycythemic. The percentage of anemia was (27.3%) in stage I disease, followed by (38.0%) in stage II, raised to (100%) in stage III then dropped to (58.33%) in stage IV.

COPD itself may cause anemia as a chronic disease, shortened survival of RBCs as a result of raised level of inflammatory mediators as IL1, IL6, CRP and TNF [8]. This might occur through shortened RBC survival, iron homeostasis dysregulation and impaired bone marrow erythropoietic response [10]. Nutritional derangements in COPD patients were proposed as a cause for anemia [11]. Also, tobacco smoking and its role in oxidative stress has a role in RBCs production [12]. Lastly, the role of comorbidities frequently encountered in COPD patients as upper GI bleeding and folate deficiency was proposed however they were largely related to smoking also [5]. This finding is common in COPD and exaggerated during exacerbation.

Contrary to this study result [5], was performed in Iran, on Eighty patients. Hemoglobin and erythropoietin levels were assessed in all patients. The results showed that anemia of chronic disease was present in (13) of 80 patients (16%). The mean serum levels of EPO were  $59 \pm 203$  (SD)  $\mu$ /l and  $70.3 \pm 255$  (SD)  $\mu$ /l in anemic and non anemic COPD patients respectively. There was an increase in EPO hormone level in non anemic COPD patients than anemic and this can be explained by apart from EPO resistance, other factors may also contribute to the lower hemoglobin level in COPD patients. Defective EPO production and impaired iron utilization due to factors other than inflammation can be responsible for anemia in COPD patients as malnutrition, tobacco smoking (because of its associated oxidative stress) and finally oxygen therapy can theoretically blunt hypoxia-driven erythropoiesis in COPD patients.



**Figure 3** Correlation between EPO hormone level and both Hemoglobin and Hct levels in groups of COPD patients.

**Table 7** Correlation between EPO hormone level and oxygen saturation during exacerbation and remission in COPD patients.

Among COPD patients	EPO (acute exacerbation)	
	R	p
O <sub>2</sub> saturation % during acute exacerbation	-0.352	<0.005
Among COPD patients	EPO (remission)	
	R	p
O <sub>2</sub> saturation % during Remission	-0.563	<0.005

In the current study we found that there were statistically highly significant increases ( $p < 0.005$ ) in EPO hormone level and oxygen saturation during remission than exacerbation (Table 5).

In agreement with this study result [13], who found that Log-Epo plasma levels were significantly lower ( $0.46 \pm 0.32$  mU/ml) in AECOPD than in stable COPD ( $1.05 \pm 0.23$  mU/ml), smokers ( $0.95 \pm 0.11$  mU/ml) and never smokers with normal lung function ( $0.92 \pm 0.19$  mU/ml) ( $p < 0.01$  each). Log-Epo increased from ( $0.49 \pm 0.42$  mU/ml) during AECOPD to ( $0.97 \pm 0.19$  mU/ml) during stability ( $p < 0.01$ ) which means that the plasma levels of Epo are reduced during ECOPD likely in relation to a burst of systemic inflammation.

This Epo down-regulation during ECOPD can be explained by the burst of inflammation that occurs during these clinical

circumstances, as shown here by a significant increase in leukocyte and neutrophil counts, as well as by the raised concentration of hsC-RP during ECOPD. Several pieces of evidence support this proposal. First, in vitro experiments have demonstrated that IL-1 and TNF-suppress Epo expression and secretion by activating the transcription factors GATA-2 and NF- $\kappa$ B [14]. Second, clinical investigations indicate that TNF-suppresses Epo secretion in patients with advanced solid tumors and chronic infection [15]. Third, Epo plasma levels in anemic patients who suffer concomitantly of other inflammatory process are often lower than expected in relation to their hemoglobin concentration [16]. Fourth and finally, a significant negative association between Epo plasma levels and both hsC-RP and neutrophils in the patients studied here. Interestingly, this inflammatory mechanism appears to overcome the regulation of EPO by oxygen, given that the hypoxemia that occurs during exacerbations of COPD would be a strong stimulus for Epo production [17].

Contrary to this study result [8], who found that EPO level in COPD was similar to that seen in control subjects, except in those patients with chronic respiratory failure, severe nocturnal desaturation or anemia in whom EPO levels were increased.

In the current study, there was a significant negative correlation between EPO hormone level and both Hemoglobin and Hct levels in COPD patients (Table 6 and Fig. 3).

These results are in agreement with [8] and [9] they found that all anemic COPD patients showed elevated erythropoietin levels. There was a significant inverse correlation between erythropoietin hormone level and hemoglobin concentration

Also [13] and [18] found the same result in their studies.

In the current study there was a significant negative correlation between EPO hormone and Oxygen saturation during exacerbation and remission. (Table 7).

In agreement with the current study [9], who found that there was a statistically significant correlation for erythropoietin with age, PaO<sub>2</sub> and SaO<sub>2</sub> in COPD patients, as he measured the level of EPO hormone in (41) patients with COPD and ten healthy age and sex matched control subjects, the results showed negative correlation between EPO hormone level and PaO<sub>2</sub> ( $p = 0.85$ ) statistically significant, and negative correlation between EPO hormone level and SaO<sub>2</sub> ( $p = 0.99$ ).

This can be explained by diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase. As the PaO<sub>2</sub> of the plasma, and function of the hematocrit decreases, EPO hormone concentration will increase [19].

In agreement with this study also [20], investigated the early changes in erythropoietin (EPO) formation in humans in response to hypoxia. EPO levels during hypoxia were significantly elevated.

## Conclusions

EPO hormone level was significantly higher in COPD patients than in control groups. It was significantly higher in grade (II, III) than grade (I, IV) COPD patients, and during remission than during exacerbation of COPD. Anemia is more in COPD patient group than in the control group, COPD with anemia was higher in stage (II, III) than in stage (I, IV). EPO hormone

level was significantly higher in anemic than non anemic COPD patients. There is a significant negative correlation between EPO hormone level and Oxygen saturation and both HB & Hct levels in COPD patients.

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