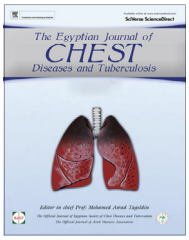
Egyptian Journal of Chest Diseases and Tuberculosis (2012) **61**, 53–57

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com



ORIGINAL ARTICLE

Study the relationship of erythropoietin and chronic obstructive pulmonary disease

R.I. El-Korashy [a], Y.M. Amin [a,*], H.A. Moussa [a], I. Badawy [b], S.M. Bakr [c]

[a] *Faculty of Medicine, Cairo University, Egypt*
[b] *Faculty of Biotechnology, Misr University for Science and Technology, Egypt*
[c] *Faculty of Medicine, Fayoum University, Egypt*

Received 15 April 2012; accepted 25 April 2012
Available online 30 January 2013

KEYWORDS

COPD;
Erythropoietin;
Anemia

Abstract *Rationale:* 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. Revealing the changes which occur in erythropoiesis in response to COPD was the aim of the current study.

Methods: 41 COPD patients of different groups according to the inclusion and exclusion criteria and ten healthy control subjects age and sex matched were enrolled in the study. For all, history taking and full Clinical exam were performed, also ABGs, PFT (spirometry), routine labs (CBC, liver and renal function) and determination of EPO should be performed on human serum by ELISA.

Results: Showed that the erythropoietin level was 15.24 ± 2.6 in stage 1, 22.61 ± 5.68 in stage 2, 33.59 ± 4, in stage 3, then 17.9 ± 3.3 in stage 4. Also the total percentage of anemia in COPD patients was 46.3% (19/41), in comparison to 51.3% (21/41) non anemic and 2.4% (1/41) polycythemic.

And that the percentage of anemia was 27.3% in stage 1, followed by 38.0% in stage 2, 100% in stage 3 then dropped to 58.33% in stage 4 with emergence of polycythemia in 8.33% of cases.

Conclusion: Although COPD was thought to cause polycythemia, the current study showed that almost half of patients have anemia, and polycythemia occurred only in the advanced stages.

It also appeared that response to erythropoietin in COPD is probably blunted especially with increased severity of the condition. This might be considered as a contributing factor in the development of anemia in COPD which is considered as anemia of chronic disease.

* Corresponding author. Tel.: +2-01117766220.
E-mail address: Ymasoliman@yahoo.com (Y.M. Amin).

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

ELSEVIER Production and hosting by Elsevier

Introduction

COPD is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years, and die prematurely from it or its complications [1].

It was estimated that 6% of the adult population were diagnosed as having COPD [2]. COPD was estimated to become

0422-7638 http://dx.doi.org/10.1016/j.ejcdt.2012.10.026

the third leading cause of death and fifth cause of disability by the year 2020 [3].

Although the GOLD 2011 definition of COPD did not point to the extrapulmonary consequences of COPD as the previous definition; still COPD might be considered a disorder associated with extrapulmonary effects caused by comorbidities that are either secondary to inflammatory burden of COPD or occurring in association with COPD due to sharing of same risk factors [4].

It has long been known that COPD causes polycythemia secondary to erythrocytosis caused by hypoxia present in advanced cases of COPD [5]. However, it was shown in several studies that some COPD patients had anemia rather than erythrocytosis [6,7]. Several hypotheses were proposed for this finding: for example it was thought that the inflammatory burden of COPD caused anemia of chronic disorders due to the effects of IL-1 and TNF-α (anemia in COPD), also CRP and IL-6 [8]. This might occur through shortened RBC survival, iron homeostasis dysregulation and impaired bone marrow erythropoietic response [3]. Nutritional derangements in COPD patients were proposed as a cause for anemia [9]. Also, tobacco smoking and its role in oxidative stress has a role in RBCs production [10]. 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 [7].

EPO is an endogenous glycoprotein hormone that serves as the primary stimulus for erythropoiesis. The kidney is the primary site of EPO production, but the liver also produces the hormone. EPO acts in the bone marrow, where it promotes terminal differentiation of progenitor cells into erythrocytes [11].

Diminished arterial oxygen content associated with anemia or hypoxia is the major stimulus for EPO production and usually produces an exponential increase [12].

Ninety percent of EPO is produced in the peritubular cells of the adult kidney in response to a decrease in tissue oxygenation [13].

There is evidence indicating that the protein on these cells which detects oxygen saturation of the blood is a heme-containing moiety [14]. As the pO2 of the plasma, a function of the hematocrit decreases, EPO concentration will increase [15].

The hematocrit is one of the most precise methods of determining the degree of anemia or polycythemia (excessive amount of red blood cells) [16]. The hematocrit represents the volume of red blood cells in 100 ml of blood and is therefore reported as a percentage [17]. Anemia is not a disease, but a term indicating insufficient hemoglobin to deliver oxygen to the cells. It is always a secondary phenomenon [3]. Optimum values in an adult male are: Hemoglobin 14–18 gm/dL and hematocrit 40.0% to 54.0% [18].

Rationale

There is a debate about the changes which occur in erythropoiesis in response to COPD. Some patients have anemia and others have polycythemia, thus the study was performed to assess the changes in erythropoietin in COPD patients in different stages.

Subjects and methods

This study was performed in Kasr Al-Aini hospital, Cairo University. The study included 51 subjects, 41 COPD patients of different groups and ten healthy control subjects, age matched.

Inclusion criteria:

– Patients diagnosed as COPD and categorized according to the GOLD criteria 2011.

Exclusion criteria:

- History of asthma.
- History of malignancy or haematologic disorder.
- Systematic or autoimmune disorder.
- Thyroid disease.
- Liver cirrhosis.
- Heart failure (ejection fraction $< 55\%$).
- History of gastrointestinal or other hemorrhage.
- Renal failure (serum creatinine > 1 gm/dL).
- Blood transfusion in the last 4 months.

For all subjects the following were done.
History taking and full Clinical exam.
Arterial blood gases.
Pulmonary function test; spirometry.
Routine labs (CBC, liver and renal function).

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

Collect 1 mm of whole blood without anticoagulantion in the morning between 7:30 a.m. to 12:00 noon, because diurnal variation of erythropoietin has been reported [19,20]. 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 months [21].

Results

This study was performed in Kasr Al Aini hospital in collaboration with the Clinical pathology department, and Biochemistry department in the Faculty of Biotechnology, MUST.

The study included 51 male subjects divided as 41 COPD patients of different groups and 10 healthy control subjects.

Discussion

The study was aiming at assessment of the erythropoietin changes in different stages of COPD as COPD is traditionally associated with polycythemia [7] also the assumption that anemia frequently occurs in patients with COPD [8]

51 subjects were included in this study, divided into 41 COPD male patients aged 56. 64 + 7.04 selected according to the inclusion and exclusion criteria mentioned before and 10 healthy age matched males as control group.

The descriptive data in Table 1 showed that the mean hemoglobin for COPD cases was 13.82 ± 1.95 g/dL while for the control it was 14 ± 1.27 g/dl with no statistical significant. Mean value of Hematocrit was 42.1 ± 6.09 for COPD and 43.8 ± 3.19 for control and again result was not statistically significant. However oxygenation parameters in ABGs showed statistically significant difference between the COPD patients and the control group as PaO2 was 58.56 ± 16.05 and 81.5 ± 2.54 for COPD cases and control, respectively and SaO2 was 84.9 ± 14.7 and 96.80 ± 1.40 for COPD cases and control respectively.

Table 1 Comparison between mean of different parameters in COPD cases and healthy control.

	COPD cases group	Healthy controls	Mann–Whitney test	
			U value	P value
Age	56.65 ± 7.04	53.60 ± 9.3	138	0.481
Hgb	13.82 ± 1.95	14 ± 1.27	127	0.316
Rbcs	4.84 ± 0.88	5.11 ± 0.46	156	0.829
Hct	42.1 ± 6.09	43.8 ± 3.19	163	0.978
Ph	7.42 ± 0.55	7.40 ± 0.011	103	0.097062
PCO2	44 ± 14.94	40.40 ± 1.96	109	0.136405
PO2	**58.56 ± 16.05**	**81.5 ± 2.54**	**15**	**0.000055**
SO2	**84.9 ± 14.7**	**96.80 ± 1.40**	**20**	**0.000095**

Significant at p level < 0.05.

Table 2 Comparison between the erythropoietin levels in different COPD stages.

No of cases	Gold stages				Kruskal–Wallis test	
	Stage 1	Stage 2	Stage 3	Stage 4		
	11	13	5	12	Chi-square	p-value
Erythropoietin mean ± SD	15.24 ± 2.6	22.61 ± 5.68	33.59 ± 4	17.09 ± 3.3		
Erythropoietin median (IQR)	6.87 (2.04 – 19.5)	4.46 (2.75 – 11.23)	6.5 (3.06 – 77.68)	5.79 (4.41 – 64.75)	0.912	0.823

Significant difference at $p < 0.05$.

Table 3 Correlation between different parameters in control group.

Erythropoietin	CC	P value	HB	CC	P value	Hct	CC	P value
Age	0.80	**0.017**	Age	−0.63	0.092	Age	−0.40	0.32
Ph	0.32	0.445	Ph	0.50	0.20	Ph	0.32	0.45
PCO2	−0.20	0.63	PCO2	−0.6	0.09	PCO2	−0.80	**0.017**
PO2	−0.80	**0.017**	PO2	0.316	0.445	PO2	0.2	0.64
SO2	−0.80	**0.017**	SO2	0.316	0.445	SO2	0.2	0.64

Significant correlation if $p < 0.05$.

Table 4 Correlation between different parameters in COPD patients.

Erythropiotin	CC	P value	HB	CC	P value	Hct	CC	P value
Age	−0.12	−0.12	Age	−0.17	0.28	Age	−0.19	0.24
Ph	−0.18	0.26	Ph	**−0.46**	**0.002**	Ph	−0.46	0.002
PCo2	−0.21	0.18	PCo2	0.24	0.14	PCo2	**0.338**	**0.03**
PO2	0.031	0.85	PO2	−0.15	0.34	PO2	−0.19	0.24
SO2	−0.002	0.99	SO2	−0.18	0.26	SO2	−0.21	0.18
GOLD staging	0.043	0.79	GOLD staging	−0.17	0.28	GOLD staging	−0.07	0.68

Significant correlation if $p < 0.05$.

In the current study, in Table 3 results showed that there was a statistically significant correlation for erythropoietin with age, PaO2 and SaO2. However there was no statistically significant correlation between the erythropoietin level and other parameters in COPD patients as shown in Table 4. This led to the assumption that the factors that normally affect erythropoietin production are no more effective; thus it could be postulated that there would be a blunted response of erythropoietin to stimuli in COPD.

This may be explained by the presence of a two opposing forces, one in its way to increase the production in response to hypoxia resulting in polycythemia. The other one being a chronic disease with systemic inflammatory burden, there is an impact on bone marrow and kidneys decreasing erythropoietin and production of RBCs [22]. Earlier studies showed that there is an apparent lack of polycythaemic response to hypoxaemia in COPD [23], John et al., found that there was a significant inverse correlation of haemoglobin versus erythropoietin, indicating the presence of erythropoietin resistance. The association of inflammation and erythropoietin resistance is typical of anemia of chronic disease [8].

COPD patients were divided into four stages according to the GOLD 2011 and erythropoietin was correlated to degree of severity of COPD in Table 2. And though the results were

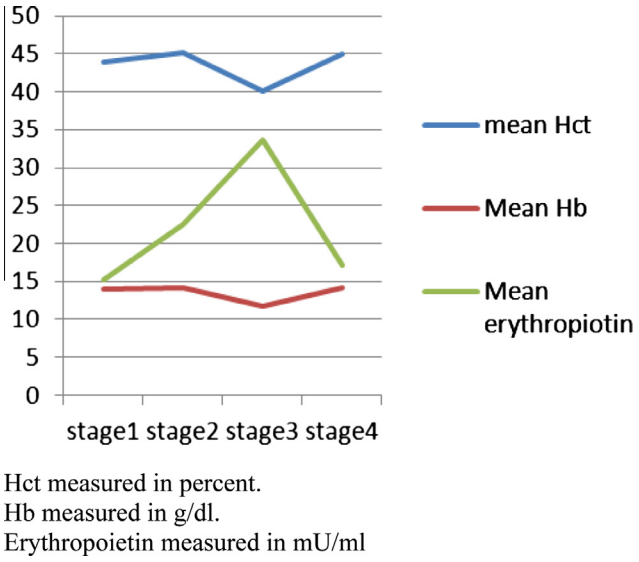


Figure 1 Comparison between the mean hematocrite, hemoglobin, and erythropiotin in different stages of COPD: Hct measured in percent. Hb measured in g/dl. Erythropoietin measured in mU/ml.

not statistically significant, it was found that in stage one erythropoietin remains low (15.24 mU/ml) and increases gradually throughout stage two (22.61 mU/ml) to reach a maximum level in stage three (33.59 mU/ml). Then a decrease followed in stage four (17.09 mU/ml) as shown also in Fig. 1.

On reflecting these changes on the routinely measured parameters of complete blood picture, the percentage of anemia in stage 1 was 27.3% and increased to 30.8% in stage 2, reaching 100% in stage 3 dropping again to 58.33% in stage 4. This pattern occurs with hematocrit changes as shown in Fig. 1.

This picture reflects an increase in the erythropoietin throughout COPD stages in response to increase percentage of anemia throughout the same stages till a certain point where evident normalization of the hemoglobin level occurs in stage 4 associated with the appearance of polycythemia with secondary drop in the erythropoietin level. So, it would be possible that the normalization of hemoglobin may be due to phasic change in hemoglobin levels from anemia to polycythemia passing through normal levels of hemoglobin rather than improvement of hemoglobin.

This was also explained by the fact that with worsening of the condition there may be increased blunting of response to erythropoietin due to inflammatory burden as the plasma levels of erythropoietin are reduced in relation to a burst of systemic inflammation [24,25]. However anemia of chronic disease was proposed as a cause for anemia in COPD patients and inflammation may not be the only cause as renal impairment, even with normal creatinine level may cause decreased production of erythropoietin [26].

Polycythemia may be caused by acidosis, whether metabolic due lactic acidosis or respiratory due to chronic respiratory failure [27], and not only due to hypoxia which itself can cause lactic acidosis and produces a vicious circle with inflammation and oxidative stress [28].

In a similar study performed in Iran, the authors worked on 80 patients with mean age 66.48 ± 11.55 and found anemia in 13 of the 80 patients (16%), while in the study in hand the percentage of anemia in COPD patients was 46.3% (21 patients) of the COPD patients had anemia (< 13.5 g/dL) as shown in Table 5 [7].

In a study performed by John et al., anemia was diagnosed in 13% of 101 COPD patients [8]. All anemic COPD patients showed elevated erythropoietin levels (41.8 ± 25.4 U/L vs 16.3 ± 2.9 U/L); with a significant inverse correlation of hemoglobin versus erythropoietin ($p < 0.01$) [8]. This finding supports the idea of increase the erythropoietin with anemia as happened in COPD stages 1, 2, and 3 according to the GOLD, 2011.

Conclusion

Although COPD was thought to cause polycythemia, the current study showed that almost half of patients have anemia, and polycythemia occurred only in the advanced stages. It also appeared that reponse to erythropoietin in COPD was probably blunted especially with increased severity of the condition. This might be considered as a contributing factor in the development of anemia in COPD which was considered as anemia of chronic disease.

References

[1] Global initiative for Obstructive Lung Disease (GOLD), Introduction, 2011, p. vii.
[2] R.J. Halbert, J.L. Natoli, A. Gano, E. Badamagran, A.S. Buist, D.M. Mannino, Global burden of COPD: systemic review and meta-analysis, Eur. Respir. J. 28 (2006) 523–532.
[3] G. Weiss, L.T. Goodnough, Anemia of chronic disease, N. Engl. J. Med. 352 (2005) 1011–1023.
[4] L.M. Fabbri, F. Luppi, B. Beghe, K.F. Rabe, Complex chronic comorbidities of COPD, Eur. Respir. J. 31 (2008) 204–212.
[5] J.A. Wedzicha, R.M. Rudd, M.C. Apps, F.E. Cotter, A.C. Newland, D.W. Empey, Erythrapheresis in patients with

Table 5 Pattern of hemoglobin levels in different COPD stages.

COPD stages	Hb						Total
	Anemic		Normal		Polycythemic		
	No	% of stage	No	% of stage	No	% of stage	
I	3	27.3	8	72.7	0	0	11
II	4	30.8	9	69.2	0	0	13
III	5	100	0	0	0	0	5
IV	7	58.33	4	33.33	1	8.33	12
Total and percentage	19	46.3	21	51.3	1	2.4	41 (100%)

polycythaemia secondary to hypoxic lung disease, Br. Med. J. 286 (1983) 511–514.
[6] T. Similowski, A. Agustı, W. MacNee, B. Schonhofer, The potential impact of anaemia of chronic disease in COPD, Eur. Respir. J. 27 (2006) 390–396.
[7] D. Attaran, M. Khajedalouee, F. Ahmadi, F. Rezaeitalab, M. Towhidi, A. Asnaashari, M. Babaeian, S. Rezaei, S. Lari, Anemia in COPD patients and its relation to serum levels of erythropoietin, Tanaffos 8 (2) (2009) 11–16.
[8] M. John, S. Hoernig, W. Doehner, D.D. Okonko, C. Witt, S.D. Anker, Anemia and inflammation in COPD, Chest 127 (2005) 825–829.
[9] W. Aniwidyaningsih, R. Varraso, N. Cano, C. Pison, Impact of nutritional status on body functioning in chronic obstructive pulmonary disease and how to intervene, Curr. Opin. Clin. Nutr. Metab. Care 11 (4) (2008 July) 435–442.
[10] P.M. Calverley, R.J. Leggett, L. McElderry, D.C. Flenley, Cigarette smoking and secondary polycythemia in hypoxic cor pulmonale, Am. Rev. Respir. Dis. 125 (1982) 507–510.
[11] A.J. Erslev, Erythropoietin, N. Engl. J. Med. 324 (1991) 1339–1344.
[12] W. Jelkmann, Erythropoietin: structure, control of production and function, Physiol. Rev. 72 (1992) 449–489.
[13] S.T. Koury, M.C. Bondurant, M.J. Koury, Localization of erythropoietin synthesizing cells in murine kidney by in-situ hybridization, Blood 71 (1988) 524–527.
[14] M.A. Goldberg, S.P. Dunning, H.F. Bunn, Regulation of the erythropoietin gene: evidence that the oxygen sensor is a heme protein, Science 242 (1988) 1412–1415.
[15] A.J. Erslev, J. Caro, G. Birgegard, R. Silver, O. Miller, The Biogenesis of Erythropoietin, Exp. Hematol. (1980) 1–13, Suppl 8.
[16] W. Schmidt, B. Bermann, P. Winchenbach, S. Lison, D. Boning, How valid is the determination of hematocrit values to detect blood manipulation?, Int J. Sports Med. 21 (2) (2000) 133–138.
[17] J.E. Greenleaf, V.A. Convertino, G.R. Mangseth, Plasma volume during stress in man: osmolality and red cell volume, J. Appl. Physiol. 47 (5) (1979) 1031–1038.
[18] H.H. Billett, in: H.K. Walker, W.D. Hall, J.W. Hurst (Eds.), Clinical methods: The History, Physical, and Laboratory Examinations, third ed., Butterworth, Boston, 1990.
[19] L. Wide, C. Bengisson, G. Birgegard, Circadian rhythm of erythropoietin in human serum, Br. J. Hematol. 72 (1989) 85–90.
[20] J.L. Spivak, Erythrocytosis, Hematology: Basic Principles and Practice, in: R. Hoffman, E.J. Benz, Jr., S.J. Shattil, B. Furie, H.J. Cohen, L.E. Silberstein, 1995;Chapter 37, pp. 484-491.
[21] DRG® EPO (Erythropoietin) ELISA (EIA-3646) July, 2007 brochure Web. Available from: www.drg-international.com.
[22] Y. Nussbaumer-Ochsner, K.F. Rabe, Systemic manifestations of COPD, Chest 139 (2011) 165–173.
[23] E.F. Baldwin, A. Cournand, D.W. Richards (Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema), Medicine 28 (1949) 201–210, Quated from T. Similowski, A. Agustý, W. MacNee, B. Schonhofer, The potential impact of anaemia of chronic disease in COPD, Eur. Respir. J. 27 (2006) 390–396..
[24] Ernest Sala, Catalina Balaguer, Cristina Villena, Angel Ríos, Aina Noguera, Belén Núñez, Alvar Agustí (Low erythropoietin plasma levels during exacerbations of COPD), Respiration 80 (3) (2010) 190–197.
[25] Alan J. DeAngelo1, David G. Bell2, Michael W. Quinn1, Deborah Ebert Long3, Daniel R. Ouellette, Erythropoietin response in critically ill mechanically ventilated patients: a prospective observational study, Critical Care (2005).
[26] Raffaele Antonelli Incalzi, Andrea Corsonello, Claudio Pedone, Salvatore Battaglia, Giuseppe Paglino, Vincenzo Bellia, Chronic renal failure a neglected comorbidity of COPD, Chest 137 (2010) 831–837.
[27] Cosimo Marcello Bruno, Maria Valenti (Acid-Base disorders in patients with chronic obstructive pulmonary disease: a pathophysiological review), J. Biomed. Biotechnol. 2012 (2012) 8.
[28] Victor Kim1, Joshua O. Benditt2, Robert A. Wise3, Amir Sharafkhaneh, Oxygen therapy in chronic obstructive pulmonary disease, Proc. Am. Thorac. Soc. 5 (2008) 513–518.