

Anemia in COPD: Should It Be Taken Into Consideration?

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Recent recognition of the importance of nonpulmonary signs and symptoms in the management and prognosis of chronic obstructive pulmonary disease (COPD) has led to a shift in the focus of diagnostic and therapeutic strategies to encompass these aspects. We no longer concentrate on assessing a single functional variable (forced expiratory volume in 1 second) as a predictor of survival in these patients. Most of the research undertaken to date into COPD-related systemic disorders has targeted weight loss, muscular dysfunction, osteoporosis, and cardiovascular disease. However, the abnormal inflammatory response associated with COPD may provoke other disorders such as anemia. Moreover, comorbid anemia has been shown to be an independent predictor of mortality in several chronic diseases including cancer and heart failure. Anemia is, therefore, an entity that should be taken into consideration in the overall management of respiratory disease because it may have a clear detrimental impact on various aspects of the patient's health, including dyspnea, exercise tolerance, and quality of life.

There is a growing body of literature on the relationship between anemia and COPD. Our aim is to briefly review the pathophysiologic aspects of this association before going on to discuss some of the most recent evidence published.

Key words: Anemia. COPD. Erythrocytosis.

The primary functions of the cardiorespiratory system are to deliver oxygen and substrates to cells and to eliminate the waste products of cell metabolism.¹ The oxygen essential for tissue metabolism is delivered by red blood cells containing hemoglobin, the principal oxygen transport molecule. Any decrease in hemoglobin levels results in a corresponding decrease in the oxygen-carrying capacity of the blood (anemic hypoxia). Thus, while PaO₂ may

La anemia en la EPOC. ¿Debemos pensar en ello?

El reconocimiento reciente de la importancia que tienen las manifestaciones extrapulmonares, tanto en el manejo como en el pronóstico de la enfermedad pulmonar obstructiva crónica (EPOC) ha llevado a que reconduzcamos las estrategias diagnósticas y terapéuticas hacia ellas, y que no centremos nuestros esfuerzos en valorar sólo una variable funcional (el volumen espiratorio forzado en el primer segundo) como marcador de supervivencia en estos pacientes. Los trastornos sistémicos relacionados con la EPOC más estudiados son la pérdida de peso, la disfunción muscular, la osteoporosis y la enfermedad cardiovascular. Sin embargo, hay otros posibles efectos, como el síndrome anémico, que también podría ser consecuencia de la anormal respuesta inflamatoria que se produce en esta enfermedad. Por otra parte, la anemia como comorbilidad asociada a ciertas enfermedades crónicas, caso del cáncer y de la insuficiencia cardíaca, ha demostrado actuar como un marcador de mortalidad independiente. Se trata, por lo tanto, de una entidad que debe tenerse en cuenta en el manejo integral del paciente respiratorio, ya que puede tener un impacto claramente perjudicial en diversos aspectos de la enfermedad, como la disnea, la tolerancia al ejercicio y la calidad de vida.

En la literatura médica hay un número creciente de estudios que abordan la relación entre la anemia y la EPOC. Esta revisión se centrará en revisar brevemente los aspectos fisiopatológicos relacionados con el tema y en discutir algunas de las últimas evidencias publicadas hasta el momento.

Palabras clave: Anemia. EPOC. Eritrocitosis.

remain normal, the absolute amount of oxygen transported per unit blood volume declines. The most sensible way to diagnose anemia in a patient would therefore be to directly measure the amount of oxygen delivered to peripheral tissues.² Since this is impossible, we must make a functional diagnosis based on the alterations observed in the normal process of erythropoiesis—the production, maturation, survival, and morphology of red blood cells—and on the measurement of circulating iron levels.

The World Health Organization defines anemia as a hemoglobin level less than 13 g/dL in men and 12 g/dL in women.³ To enable proper functioning of basal erythropoiesis, the peritubular cells of the kidney secrete small quantities of erythropoietin (EPO) daily. This hormone inhibits the apoptosis of red blood cells and

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stimulates their proliferation and differentiation into normoblasts in hematological tissue.⁴ When hemoglobin levels fall below 10.5 g/dL, new cells mobilize and EPO titers increase logarithmically. The chief trigger for EPO production is the availability of oxygen in tissues, and its genetic transcription is mediated by the hypoxia inducible factor. Therefore, one of the compensatory mechanisms for prolonged hypoxia is secondary erythrocytosis caused by an increase in EPO. This phenomenon has been reported in low-oxygen environments (such as high altitudes) and in cases of hypoxemia associated with cardiopulmonary diseases.¹ A hematocrit level higher than 54% is the most widely accepted diagnostic criterion.

Iron uptake also plays a key role in hematopoiesis.⁵ Most of the iron comes from senescent erythrocytes and is recycled by the reticuloendothelial system and transported in plasma by transferrin. Most of these iron-loaded transferrin molecules bind to specific receptors located on the surface of the erythroid precursors (soluble transferrin receptors) and are engulfed by the cell. Once the iron has been released, the receptor-transferrin complex returns to the cell surface and the transferrin molecules return to circulation to be used again. The iron released inside the cells is used to synthesize hemoglobin, and any excess is deposited in the form of ferritin.

Anemia in COPD

The prevalence of anemia in the general population increases with age, and the condition described as anemia of inflammation or anemia of chronic disease is found in many diseases (such as cancer and rheumatoid arthritis). Thus we may infer that patients with COPD will fulfill these conditions since COPD is a chronic inflammatory disease that affects an aging population. However, we should also bear in mind that anemia in older patients is usually multifactorial and in COPD it can also be the result of a number of factors, such as nutritional disorders, occult blood loss, treatment with certain drugs (theophylline or angiotensin-converting enzyme inhibitors), and even oxygen therapy.⁶

One of the first studies to investigate anemia in patients with COPD was published by Tassiopoulos and colleagues in 2001.⁷ Their initial objective was to study the characteristics of anemia and assess the compensatory erythropoietic response in clinically stable patients with idiopathic pulmonary fibrosis or COPD in respiratory failure. The assumption was that the hematologic mechanism would function differently in these 2 diseases and that the phenomenon of secondary erythrocytosis would be retained in COPD in the presence of chronic hypoxemia. However, they found that the expected response (an increase in red cell mass) was inconsistent in a subgroup of patients with COPD. These individuals had normal or below normal hemoglobin values in spite of higher than normal concentrations of EPO in plasma, an indication that inflammation was probably the cause of the inconsistent response. These findings were confirmed by a recent study of 101 patients with COPD,

13% of whom were anemic.⁸ In that study, patients fulfilling the criterion for anemia had higher levels of EPO than nonanemic COPD patients as well as more elevated values in certain other inflammatory parameters, such as interleukin (IL) 6 and C-reactive protein. Moreover, an inverse correlation was found between hemoglobin and EPO levels, an indication of the existence of a certain resistance to the action of this hormone. These results, and the lack of any correlation between anemia and the nutritional abnormalities found in these patients (weight loss and cachexia), led the authors to conclude that the development of anemia in patients with COPD fulfills the criteria for anemia of chronic disease. This conclusion can be reasonably sustained on the basis of the ample scientific evidence available on the complexity of the inflammatory response and oxidative stress associated with COPD. These processes involve various types of cells (neutrophils, macrophages, and T-lymphocytes) and a wide variety of proinflammatory mediators (including tumor necrosis factor [TNF- α] and its receptors, leukotriene B₄, IL-1, IL-6, IL-8, C-reactive protein, and fibrinogen^{9,10}). Levels of these mediators are elevated in both peripheral blood and sputum in these patients and become even higher during exacerbations.^{5,9-11} To date, the relationship between them and the sequence of events observed remains poorly understood. However, it is known that the intensity of systemic inflammation is directly proportional to disease severity.^{12,13}

Anemia of Chronic Disease, or Anemia of Inflammation

Anemia of chronic disease is an immune disorder that has been reported in numerous diseases with an inflammatory component. Inflammatory cytokines have various effects that play a key role in the pathogenesis of this form of anemia and ultimately interfere with the normal mechanisms of erythropoiesis. The following possible mechanisms have been proposed:

1. Dysregulation of iron homeostasis caused by the accumulation and retention of iron within cells of the reticuloendothelial system giving rise to a consequent decrease in available iron for use by progenitor cells. The administration of IL-1 and TNF- α has been shown to lead to the development of hypoferrremia in experimental animals.¹⁴

2. Impaired proliferation of erythroid precursors. The most potent inhibitor is interferon- γ , although the free radicals generated by oxidative stress also have this effect. This phenomenon can result in an increase in the apoptosis of these cells or a decrease in the expression of EPO in their receptors.

3. Impaired bone marrow response to EPO caused directly by cytokines. IL-1 and TNF- α inhibit the expression of this hormone in vitro. Finally, the activation of these mediators may stimulate the production of hepcidin, a recently discovered polypeptide synthesized in the liver that participates in the process of iron absorption and is thought to play a key role in the development of anemia of chronic disease¹⁴ (Figure 1).

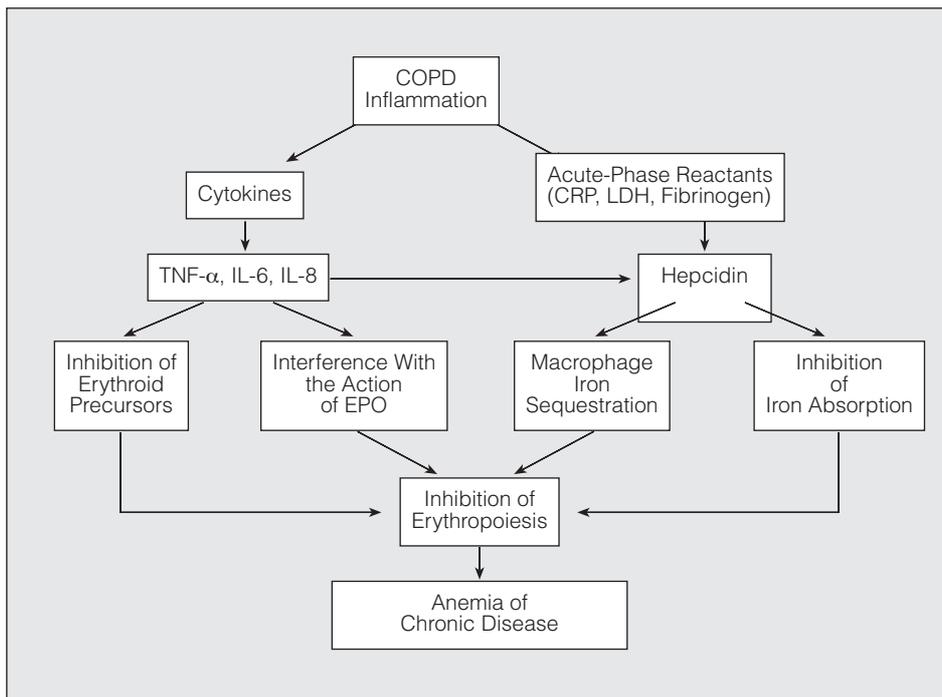


Figure 1. Possible mechanisms of anemia of inflammation, or anemia of chronic disease, in chronic obstructive pulmonary disease (COPD). EPO indicates erythropoietin; IL, interleukin; LDH, lactate dehydrogenase; CRP, C-reactive protein; and TNF- α , tumor necrosis factor α .

Alterations in Hematopoiesis in COPD

Macrocytosis

An increase in mean corpuscular volume (MCV) is reported in patients with COPD, although the cause is still poorly understood. To investigate this phenomenon, Tsantes et al¹⁵ studied 32 clinically stable patients with COPD and hypoxemia and 34 healthy volunteers. They evaluated the following parameters: complete blood count, percentage of F-cells (erythrocytes containing fetal hemoglobin), arterial blood gases, and EPO levels. Macrocytosis (defined as MCV>94 fL) was found in almost half of the patients with COPD (43.75%), and 37% of this group had erythrocytosis. The EPO response was not associated with the degree of hypoxemia, erythrocytosis, or macrocytosis, and in some cases the phenomenon occurred independently. The F-cell percentage was significantly higher in the patients with COPD, and this parameter correlated with MCV values. On the basis of these findings, the authors hypothesized that erythropoietic stress occurs repeatedly in COPD as a result of exacerbations and nocturnal or exercise-related desaturation, and that this triggers, as a compensatory mechanism, the release of immature cell forms in the bone marrow to optimize oxygen carrying capacity. Even when they are within the normal range, hemoglobin concentrations can be suboptimal in these patients given the severity of their baseline hypoxemia. These findings once again confirm that the phenomenon of secondary erythrocytosis does not occur consistently in all COPD patients, and that increases in hematocrit and red cell mass are often not so high when they are compared to those found in individuals living at high altitudes.

In a recent study of macrocytosis in 58 patients with COPD who were not hypoxemic, García Pachón and

Padilla-Navas¹⁶ analyzed the possible relationship between this phenomenon and other function parameters. The prevalence of macrocytosis in that study was 29%. No correlation was found between MCV and arterial oxygen saturation, a result similar to that of the study discussed above. The most interesting finding, however, was a significant correlation between macrocytosis, dyspnea, and forced expiratory volume in 1 second in a subgroup of 9 ex-smokers (36%), a finding that suggests a correlation between macrocytosis and a deterioration in the clinical situation.

Various clinical and experimental observations have shown that COPD causes neurohumoral activation, which presumably contributes to the self-perpetuating pathogenic cycle of this disease and is related to its systemic effects.¹⁷ It has been suggested that alterations in the activation of the renin-angiotensin-aldosterone system could in part help to explain the inconsistencies found with respect to erythrocytosis in patients with COPD (Figure 2). There may be an association between the activation of this system and polycythemia in certain clinical conditions, including severe heart failure, kidney transplant, chronic hemodialysis, and renovascular arterial hypertension.¹⁸ Vlahakos et al¹⁹ even observed an increase in EPO secretion in experimental animals after administration of renin or angiotensin II. Thus, administration of angiotensin-converting enzyme inhibitors is accompanied by a reduction in EPO and hematocrit values. In this study, the authors analyzed the degree to which activation of this system was associated with the development of compensatory erythrocytosis in hypoxemic COPD patients. Renin and aldosterone levels were 3 times higher in the patients with erythrocytosis than in the control group of hypoxemic COPD patients who did not have erythrocytosis. No

intergroup differences were found in serum EPO levels, while renin levels and PaO₂ were the only variables associated with hematocrit values. The absence of any association between EPO and hematocrit values points to the existence of another mechanism for the development of polycythemia, such as, for example, the direct action of angiotensin II. This hormone would induce sustained secretion of EPO or alternatively, as it is recognized as a growth factor for various cell types, it would act on erythroid precursors, favoring their proliferation. Based on their findings, the authors hypothesized that the variability found in parameters relating to red cell mass in COPD patients presenting a similar degree of hypoxemia may depend in part on the integrity of the renin-angiotensin-aldosterone-system.¹⁹

Other Factors

Renal flow. As EPO is synthesized primarily in the kidney, any impairment of renal hemodynamics—a comorbidity also reported in COPD as a consequence of decreased renal blood flow—causes an imbalance in the supply and demand of oxygen that affects the production of this hormone possibly as a result of an effect on the oxygen sensor.²⁰

Medication. It has been observed that, like the angiotensin-converting enzyme inhibitors, which reduce hematocrit values, theophylline also gives rise to a reduction in the production of red blood cells. The suppression mechanism is complex and in principle may be the result of direct inhibition of erythropoiesis through apoptosis induced by this drug rather than any effect on EPO.²¹ In contrast, phenoterol, a β_2 -agonist used to treat COPD, directly affects the renin-angiotensin-aldosterone-system and stimulates the secretion of EPO.¹⁸

Androgens. Androgens can also stimulate erythropoiesis directly by stimulation of erythroid progenitors or indirectly by activating the renin-angiotensin-aldosterone system¹⁸; in fact, anemia is a common finding in men who have hypogonadism or are receiving antiandrogenic treatment. Furthermore, testosterone titers decline with age. There is evidence that testosterone concentrations are low in men with COPD.²² Various predisposing factors for these low values have been proposed, including hypoxia, corticosteroid treatment, and the chronic nature of the disease. A recently published study of a sample of 905 patients over 65 years of age concluded that low testosterone levels are associated with a higher risk of developing anemia.²³

Exacerbations. Exacerbations are an adverse event occurring frequently in the natural course of disease in patients with COPD. As mentioned above, exacerbations are characterized by an increase in inflammatory markers, a development that may interfere with the hematopoietic process. Moreover, exacerbations requiring hospitalization can alter the baseline hemoglobin value, since a reduction in this value during hospitalization for various reasons has been reported.

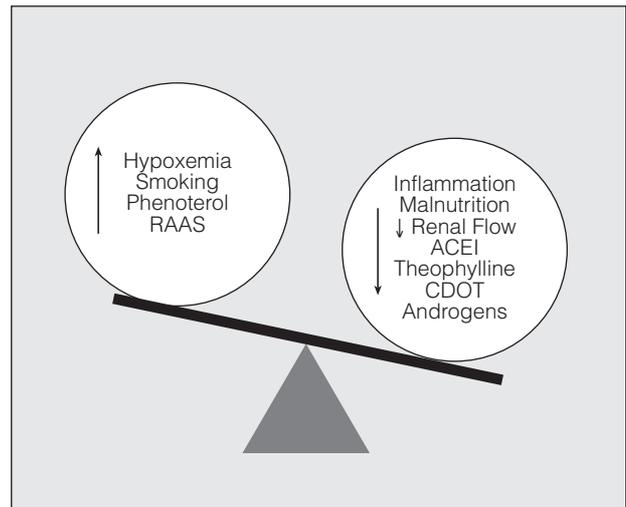


Figure 2. Factors related to erythrocytosis in COPD. ACEI indicates angiotensin-converting enzyme inhibitors; CDOT, chronic domiciliary oxygen therapy; and RAAS, renin-angiotensin-aldosterone system.

Relationship Between Anemia and Other Cardiopulmonary Diseases

Heart Failure

Numerous studies on the relationship between anemia and heart failure have determined that the presence of anemia as a comorbidity is associated with an increase in the number of hospitalizations and readmissions²⁴ and that it is an independent predictor of mortality whose treatment improves quality of life, functional capacity, and prognosis in these patients.^{25,26} In a retrospective study of hospitalized patients, John et al²⁷ studied the prevalence of anemia in COPD as compared to other respiratory diseases (such as asthma) or other chronic diseases traditionally associated with anemia, including chronic renal insufficiency, cancer, and heart failure. They found an overall prevalence of anemia in COPD of 23%. This was comparable to the prevalence in heart failure, higher than that found in asthma, and lower than in the groups with cancer or chronic renal insufficiency. In the COPD patients, anemia was not associated with age or smoking status. This study was affected by certain limitations because it was not possible to assess the influence of certain drugs on hemoglobin values or to quantify the effect of hospitalization on blood parameters. However, there is no doubt about the value of its contribution, and the conclusion drawn by the authors was that anemia is not exceptional in patients with COPD and that its treatment could be an additional strategy that would improve their prognosis.

Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a complex clinical entity of unknown etiology that causes irreversible destruction of the alveolar units. As in COPD, high concentrations of inflammatory cytokines have been reported, and the advanced stages of the disease are characterized by progressive respiratory insufficiency. In addition to the study cited above by Tassiopoulos and

coworkers,⁷ another study by the same team analyzed the impaired erythropoietic response found in patients with IPF and studied its relationship with inflammation.²⁸ In the first of these studies,⁷ 9 patients with IPF and 34 healthy controls were enrolled. In addition to a series of blood parameters, they also analyzed serum EPO and cytokine levels and studied the development of erythroid colony-forming units (CFU-E) by culturing mononuclear cells from the participants using a number of cell culture procedures. Heat inactivated serum and serum from each group was added to these cultures. They found similar hemoglobin and EPO values in both groups in spite of the hypoxemia in the patients with IPF. Concentrations of TNF- α , IL-6, and IL-8 were significantly higher in the IPF group than in the controls. Serum from the patients with IPF inhibited CFU-E growth more than the heat inactivated serum when it was added to the cultures of cells from both groups ($P < .05$). Finally, an increase in CFU-E was observed in the cultures of cells from patients with IPF cultured in the presence of inactivated serum. These results indicate that, in patients with IPF, hypoxemia triggers the proliferation of erythroid precursors as a compensatory mechanism. However, this mechanism fails in the process of differentiation and maturation, giving rise to ineffective erythropoiesis and suboptimal EPO values. It is presumed that all these phenomena are favored to some degree by the intense inflammation that is an inherent feature of IPF.

In the later study, this team took COPD as the reference disease.²⁸ Their goal was to investigate the differences in erythropoiesis between patients with IPF and COPD by repeating the earlier experiment. Once again, they compared various blood parameters, EPO levels, and the behavior of CFU-E from both study groups and the controls in the presence of serum obtained from the study sample and heat-inactivated serum. The results of the second study confirmed the findings of the earlier work with respect to the patients with IPF, who had significantly lower hemoglobin and EPO values than the patients with COPD despite a comparable level of hypoxemia. The increase in CFU-E in the cultures of cells from patients with IPF in the presence of inactivated serum and the inhibitory influence of the IPF patients' serum on CFU-E growth were not observed in the COPD group. In conclusion, this study confirms the presence of elevated EPO levels in patients with COPD reported in other studies—a finding that may support the hypothesis that resistance to the action of this hormone is a factor in a subgroup of patients. The importance of this study is that it was the first to investigate experimentally one of the mechanisms that had been proposed to explain the influence of inflammation on the behavior of red blood cells in COPD. It not only contributes to the effort to identify the pathogenesis of anemia in IPF, but also stimulates further research into alternative or synergistic aspects of anemia in COPD.

Cystic Fibrosis

Cystic fibrosis, which until recently was considered to be an exclusively pediatric disease, has now also become an adult disease because of the increased life expectancy

achieved in recent years. The synthesis of various inflammatory mediators (IL-1, IL-8, and TNF- α) even before colonization by *Pseudomonas aeruginosa* has been reported in these patients,²⁹ and this may be the underlying cause of the anemia.^{30,31} However, nutritional factors could also come into play, although their role would be less important since nutrition is carefully managed in the overall treatment of this disease. This point was made by O'Connor et al²⁹ in a case-control study involving 15 cystic fibrosis patients who had lower oxygen saturation values than healthy volunteers both at rest and during exercise ($P < .0001$). However, no significant intergroup differences in hemoglobin and hematocrit values were found. On the other hand, certain functional parameters related to iron kinetics were lower in the group with cystic fibrosis (serum iron, transferrin, and total iron binding capacity; $P < .05$). This would make cystic fibrosis a pulmonary disease associated with "relative anemia"—a term used to describe cases in which hemoglobin values do not reflect the hypoxemia present. It would be worthwhile to obtain confirmation of these interesting observations by way of further controlled studies.

The Effects of Anemia in COPD

It is well known that anemia is a cause per se of dyspnea and that it contributes to functional limitation in the anemic patient. However, no prospective studies have associated anemia with parameters such as dyspnea, exercise tolerance, or its impact on quality of life in patients with COPD. It is important to note that low hemoglobin concentrations can have a detrimental impact on certain respiratory variables, which improve when the anemia is corrected by treatment. Schonhofer et al^{32,33} published the only 2 studies in the literature on this subject. After treating anemia by blood transfusion in 20 patients with severe COPD in an intensive care unit, these authors observed a statistically significant reduction in minute-ventilation and work of breathing, with unloading of the respiratory muscles. The earlier study involved 5 COPD patients in whom weaning from invasive mechanical ventilation had proved difficult. By increasing hemoglobin levels to over 12 g/dL by blood transfusion, the physicians were able to extubate satisfactorily.

With respect to the repercussions of anemia on health care costs and, even more importantly, on mortality in COPD, the study by Celli et al³⁴ on the BODE score (for body mass index, airflow obstruction, and exercise is an important reference. In that study, patients who died were found to have significantly lower hematocrit levels than those who survived. One year later, the observational ANTADIR study³⁵ of a cohort of 2524 patients with COPD receiving domiciliary oxygen therapy (with a prevalence of anemia of 12.6% in men and 8.2% in women) demonstrated through multivariate analysis that a reduced hematocrit level was a strong predictor of mortality and was also associated with more frequent hospitalizations and a longer mean hospital stay. The predictors of survival in this cohort were, in descending order: age, hematocrit, body mass index, PaO₂, sex, and forced expiratory volume in 1 second. Another publication worth mentioning in this

context is one by Martínez et al³⁶ on predictors of mortality in patients with emphysema and severe airflow obstruction. In that study group, comprised of patients randomized to the medical therapy arm of the National Emphysema Treatment Trial, the authors found reduced hemoglobin to be an independent predictor of mortality together with other variables, such as age, supplemental oxygen use, higher residual volume, and higher BODE score.

Conclusions

To take almost as a dogma that hypoxemic patients with COPD are “protected” from the pathophysiological consequences of anemia by the mechanism of secondary erythrocytosis can interfere with the proper management of this condition, since, as stated repeatedly throughout this article, this phenomenon does not occur in all COPD patients. This inconsistency once again provides evidence for the heterogeneity of this disease and highlights the diversity and complexity of COPD-associated factors that can affect hematopoiesis. In COPD, we can talk about an imbalance in hemoglobinemia because there are factors that stimulate erythropoiesis (the increase in EPO in the presence of hypoxemia, nocturnal arterial oxygen desaturation, smoking, and proper functioning of the renin-angiotensin-aldosterone system) as well as others that blunt this process (inflammatory mediators, drugs, malnutrition, and oxygen therapy).

Important studies have shown anemia to be a predictor of mortality in COPD, and this is a giant step on the road to dealing with the subject and investigating, by way of controlled studies, important aspects such as the current prevalence of anemia in these patients, its pathogenesis, and its influence on symptoms, functional capacity and quality of life. Anemia should be taken into account in routine clinical practice in order to identify and, if necessary, treat the condition. However, before a treatment strategy can be devised, the prevalence and causes of anemia need to be identified, and the factors that predispose patients to it should be properly assessed. Current evidence indicates that greater importance is now being attributed to extrapulmonary manifestations of COPD and that by addressing these abnormalities we could influence the overall mortality associated with this disease.³⁷

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